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The van Ophuijsen Memorial Volume

VOLUME XII, NUMBER 3, JULY-SEPTEMBER, 1951

The present volume of the *Journal of Clinical and Experimental Psychopathology* is dedicated to the memory of Dr. van Ophuijsen and will present, during the course of 1951, reports of researches which he initiated, in which he participated, or which were in the process of completion at the time of his death, May, 31, 1950.

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Adrenocortical Responsitivity in Relation to Psychiatric Illness and Treatment with ACTH and ECT

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Tests for adrenal-cortex responsitivity give a much clearer picture of the adrenal-cortex function and the ability of the body to mobilize ACTH from the pituitary anterior lobe in health and in disease than was possible from the more or less indirect methods of estimation of the 24-hour excretion rate of cortin and 17-ketosteroids.

Although there is probably no specific psychiatric reaction associated with a particular state of the adrenal cortex, these tests have a considerable application in psychiatry, in view of the generally observed psychic concomitants of adrenal-cortex disorders.

In this communication the authors report results of investigating adrenal-cortex response in over 350 patients suffering from various psychiatric disorders, but mostly the acute psychoneurotics and acute and chronic psychotics of a modern psychiatric admission hospital.

METHOD: The response test was standardized and simplified for routine clinical use. The patients had no breakfast and fasted during the whole investigation; they were allowed to drink water at 7 A.M. and 9 A.M. Eosinophil counts in blood were made, and creatinine, uric-acid, and 17-ketosteroid estimations in urine. Eosinophils were counted immediately before and four hours after injection of 25 mg. ACTH or ingestion of 150 Gm. glucose or one electroconvulsive treatment. Urine specimens were collected for two hours before the stimulus and for four hours after. A positive response was indicated by a drop in eosino-

phils of 30 per cent and increases in uric-acid/creatine ratio of 20 per cent and in ketosteroid/creatinine ratio of 5 per cent. (It was considered to be a sign of adrenal-cortex stimulation if the diurnal drop in ketosteroid excretion which normally occurs was inhibited.) The reaction of the ACTH injection was taken as an indication of the functional activity of the adrenal cortex and its ability to respond to stimulation; reactions to glucose ingestion and to a single electroshock treatment gave evidence about the ability of the pituitary to produce ACTH endogenously.

Various combinations of test results were observed, as shown in *Table 1*, and it became clear that different adrenal-cortex activities contributed. Thus the evaluation of the test results could not be carried out in the statistical way used by Pincus, Hoagland, et al. (1949). The activity of the adrenal cortex which results in excretion of 17-ketosteroids is not necessarily the same as that responsible for the drop in eosinophil count, and the sub-

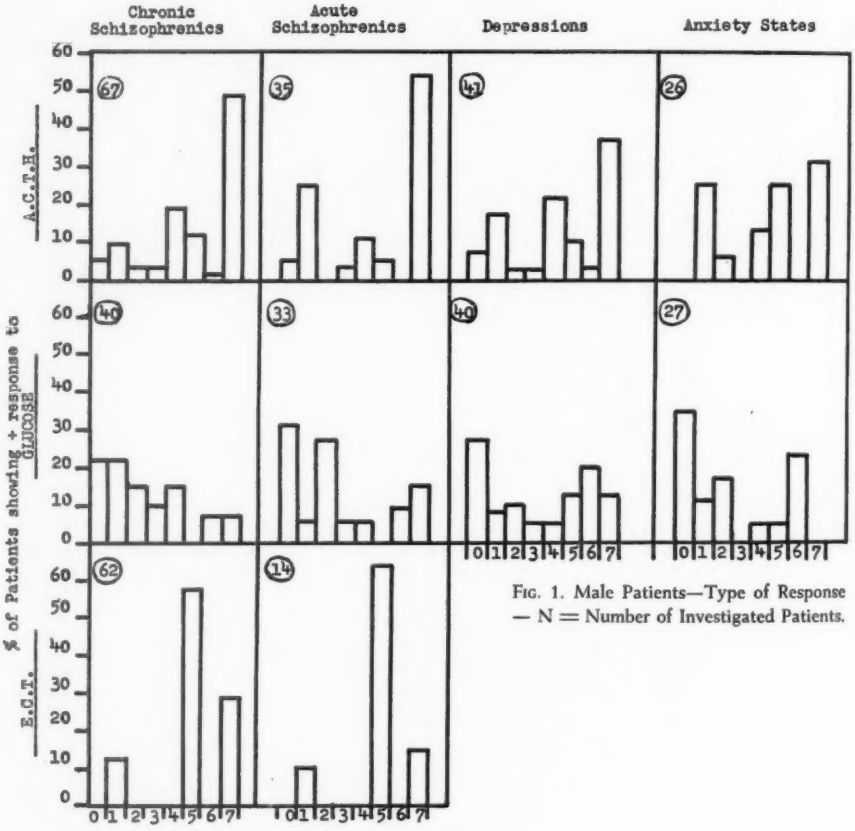

FIG. 1. Male Patients—Type of Response — N = Number of Investigated Patients.

Table 1

Reaction No.	Eosinophils.	Keto/Cr.	Uric/Cr.
0	−	−	−
1	+	−	−
2	−	+	−
3	−	−	+
4	+	+	−
5	+	−	+
6	−	+	+
7	+	+	+

stance produced by the adrenal cortex that is responsible for the alteration of uric-acid metabolism is not yet known. Excretion of 17-ketosteroids and cortin may occur independently and in some conditions in an inverse pattern (Reiss, Hemphill, Gordon, and Cook, 1949). Combination of the different responses into a single mathematical response index, as done by Pincus et al. (1949), might mask valuable information—qualitative and quantitative—about adrenal-cortex activity. Our results have therefore been classified into 8 response types (0 to 7), according to the variations in the positive or negative reactions of the different activities (Table 1).

RESULTS: Figures 1 and 2 show histograms of the eight response test types in different psychiatric disease groups. There was no appreciable difference in the distribution of extreme types of response to ACTH (0 to 7) in the different disease groups. Significantly,

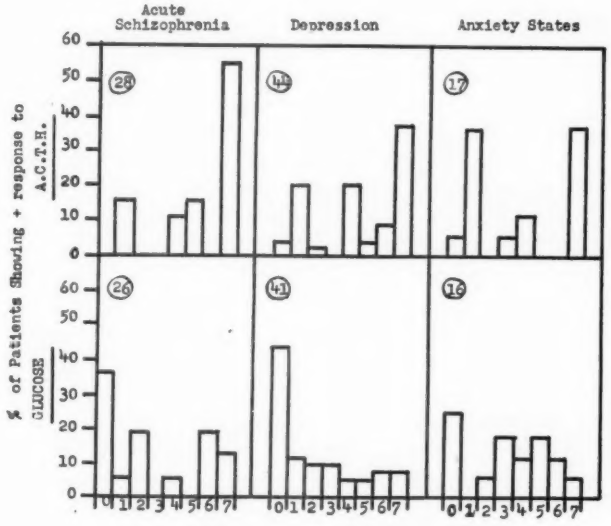

FIG. 2. Female Patients — Type of Response
N = Number of Investigated Patients.

more of the patients showed maximum response (7) to ACTH than to glucose, which means that in many the ability to mobilize ACTH endogenously was disturbed. There seemed to be an important difference between acute and chronic schizophrenics, for the latter showed significantly fewer positive responses to glucose than the former. The greatest disturbance in responsitivity among all disease groups was in male anxiety. No such case showed completely positive (7) response to glucose, while only 31 per cent showed completely positive response to ACTH, which is considerably less than the 54 per cent completely positive responses in male acute schizophrenia. A few of the patients only showed completely negative response to glucose.

When the responsitivity of the adrenal cortex to electroconvulsive therapy was tested, it was found that considerably fewer patients showed a complete response to one electric shock than to one injection of 25 mg. ACTH. On surveying the distribution of the other reaction types in the different disease entities, one sees that in the response to ACTH the distribution between the reaction types 1 to 6 was nearly identical in male and female acute and chronic schizophrenics and in male and female depressives. The reaction types 2 and 6 occurred least frequently, and the eosinophil response to ACTH was rarely disturbed. The most frequent response types after 7 were 1 and 4, where either eosinophils alone reacted or eosinophils and ketosteroids.

The distribution of the response types to glucose ingestion was very different; the most frequent type was the zero reaction, and the rarest type was reaction 5. By contrast, it is of great interest that after electroshock reaction 5 was the most frequent. Among 62 chronic schizophrenics, response types 0, 2, 3, 4, 6, were never seen after electroshock.

Figure 3 shows how the positive eosinophil, uric-acid/creatinine, and ketosteroid/creatinine responses were distributed in the disease groups. With ACTH their distribution was fairly similar in all disease groups. The distribution of the glucose responses differed from that with ACTH. The greatest incidence of positive eosinophil response occurred with ACTH, but never with glucose. The positive ketosteroid response to glucose occurred at least as frequently as the positive eosinophil response, and in acute schizophrenia, male anxiety, and male depression, more frequently. There was a similar trend of distribution of responses to electroshock and to ACTH in chronic schizophrenia, but the ratio between positive ketosteroid response and positive eosinophil response after electroshock was smaller than after ACTH.

Table 2 shows some examples of responses of individual patients to 25 mg. ACTH, 50 mg. ACTH, glucose and one electroshock treatment. Responses such as Case 9 might suggest that the actions of glucose and of electroshock are quantitatively greater than 25 mg. and less than 50 mg. of ACTH. The responses of other patients, however, showed that this is not necessarily the rule and that there are qualitative differences too. In Case 11, ACTH endogenously produced by glucose stimulation failed to reduce the eosinophil count but increased uric-acid/creatinine and ketosteroid/creatinine ratios; but in this case the injection of ACTH only reduced the eosinophil count without influencing the uric-acid/creatinine or ketosteroid/creatinine ratios. In Case 12, electroshock treatment increased the uric-acid/creatinine ratio, but ACTH was ineffective in this respect only and produced a drop

Table 2

No.	Patient	Sex	Age	Diagnosis	Response to ACTH (25 mg.)			(50 mg.)			Glucose (150 Gm.)			E.C.T.		
					Eosinophils	U/C	Keto/C	Eosinophils	U/C	Keto/C	Eosinophils	U/C	Keto/C	Eosinophils	U/C	Keto/C
1	K.T.M.	♂	24	Acute Schizophrenia	+	+	+				0	0	+	+	+	0
2	C.P.	♂	28	" "	+	0	0				0	0	+	+	+	0
3	S.V.M.	♂	25	" "	+	+	+				0	0	0	+	+	0
4	A.B.	♀	37	" "	+	0	+				+	0	0	+	+	+
5	L.O.	♀	33	" "	+	0	+				0	0	+	0	+	–
6	W.H.	♀	41	Chronic Schizophrenia	0	+	+				0	0	+	+	+	0
7	R.A.T.	♂	50	" "	0	0	+	+	0	+	0	0	0	+	+	+
8	E.T.C.	♂	26	" "	0	0	0	+	+	+	0	+	+	+	+	+
9	E.K.	♂	40	" "	+	0	0	+	+	+	+	0	+	+	+	0
10	Q.	♂	31	" "	+	0	0	+	+	+	+	+	+	+	0	0
11	W.	♂	47	" "	+	0	0	+	0	0	0	+	+			
12	B.M.	♀	66	Depression	+	0	+				0	0	0	0	+	0
13	W.	♂	43	"	+	0	0				0	+	+			
14	Ch.W.S.	♂	40	"	+	0	0				+	0	0			
15	F.B.	♂	70	"	+	0	0				0	+	+			

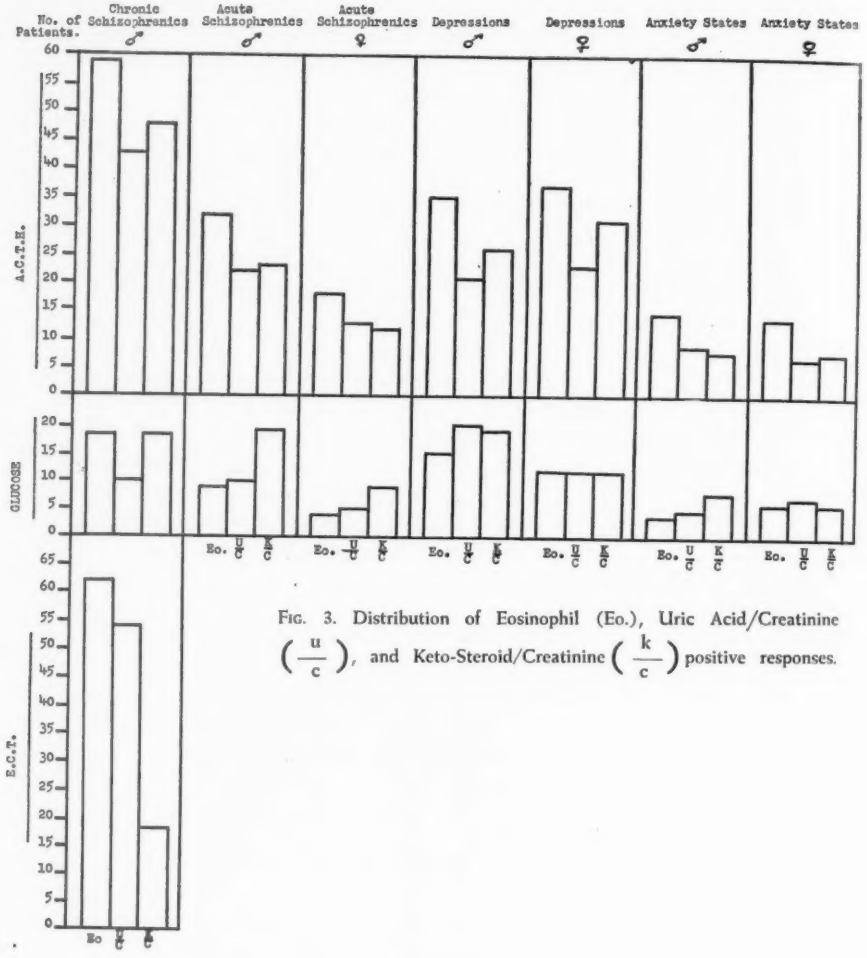

FIG. 3. Distribution of Eosinophil (Eo.), Uric Acid/Creatinine $\left(\frac{u}{c}\right)$, and Keto-Steroid/Creatinine $\left(\frac{k}{c}\right)$ positive responses.

in eosinophils and increase in ketosteroid/creatinine ratio. Qualitative differences between the response to electroshock, glucose, and ACTH were observed in many other patients.

DISCUSSION: The results of these response tests permit certain deductions about the adrenocortical-pituitary regulatory system to be made.

(1) The response types of ACTH show that different functions of the adrenal cortex can be disturbed in different degrees and in different orders. For example, it has been shown that the eosinophil response function may be normal but the adrenal unable to produce or

mobilize ketosteroids; or that the only disturbance may be that of uric-acid metabolism. Table 1, which reproduces different response types, deals with only a narrow field of adrenocortical activity, having regard to the many other adrenocortical functions which have now become known.

(2) From the response types produced by injection of glucose or by a single electroshock treatment, in patients whose response to ACTH was completely positive (reaction 7), it can be concluded that the adrenocorticotrophic hormone secreted by the anterior pituitary lobe is not necessarily indentical with the ACTH preparation injected, and the existence of an adrenocorticotrophic hormone complex, containing a number of adrenocorticotrophic hormone substances, must be assumed. These substances have different physiological reactions and can be secreted independently. Physiological evidence in support of this assumption has been previously put forward (Golla and Reiss, 1941 and 1942, Reiss, 1946).

If one considers the importance of the adrenal cortex for the normal mineral, protein, fat, and carbohydrate metabolism, and the variety of hormonal components isolated from it, some of them probably secreted by the gland as separate hormonal entities, some possibly mobilized by different adrenocorticotrophic components, it is evident that as yet very little is known about the adreno-pituitary relationship and its place in the pathophysiology of diseases. It can be assumed that there are many disorders whose relationship to the adrenocortical-pituitary regulation has not yet been recognized. There appears to be a large field of intermediate states in which there is a slight over- or underfunction of the adrenal cortex, not sufficiently pronounced to be detected on clinical grounds by the endocrinologist; and much more analytic study of hormones will have to be done before these intermediate disturbances of the adrenal cortex can be defined.

The adrenal cortex is essential to life, and it is fair to assume that adrenocortical responsitivity exercises a great influence in maintaining normal brain function. The concept that adrenocortical function prepares the organism for stress and aids or develops its ability to react, might be extended to include psychic adjustments. Such a theory was propounded by Pincus and Hoagland (1950), who believed that the repeated stress of daily life and the inability to adapt with the adrenals together contributed cumulatively to the development of psychiatric illness. They postulated that there were deficiencies—which might be genetically determined—to account for the vunerability to the stress of living of certain individuals. These people might never become mentally ill if their lives made few demands, but under conditions of inappropriate stress the endocrine defect might produce disordered brain function and eventually psychiatric illness.

This hypothesis does nothing to explain how different and contrasting psychiatric reactions are produced, and it is impossible to accept as an explanation that what has been called the original mental make-up of the patient determines the psychiatric picture. It is particularly difficult to account for good prognosis, spontaneous remissions, and the like. No doubt, however, these pathological sequences do exist, and if the response test results recorded here are considered, an adrenocortical disturbance would appear to be common in most psychiatric disorders. Failure to respond and adapt appropriately to recognizable

environmental stress is more in keeping with the conception of psychoneurosis than of affective psychoses and schizophrenia, and the response results in male anxiety are therefore particularly significant. Some negative responses may be the result of a primary disturbance of brain or may be due to the stress of severe anxiety or to the anxietylike stress produced by psychotic disturbances such as hallucinations or delusions, as in acute schizophrenia and agitation. In these cases the stress effect might vary with the intrapsychic disturbance, the nature and intensity of which, being subjective, cannot be estimated by the observer. In some cases of schizophrenia, large amounts of steroid hormones are excreted, and the values may change by as much as 200 per cent from one day to another (Reiss, Hemphill, et al. 1949). Certainly one single test injection of ACTH is not likely to alter the excretion rate of such patients significantly. Total exhaustion of the adrenal cortex can be produced by repeated stress and stimulation. This has been observed by the authors when some cases of schizophrenia were treated continuously with ACTH. Cortin and ketosteroid levels remained high for several weeks, indicating a good adrenocortical reaction, but then dropped suddenly and could not be raised, in spite of further ACTH treatment. In these cases there was mental deterioration.

It would be premature to define the clinical importance of the adrenal cortex response tests. Hoagland, Callaway, Elmadjian, and Pincus (1950) have described a statistically significant positive correlation between adrenal cortex responsitivity to pretreatment injections of ACTH and prognosis in subsequent electroshock therapy. This conclusion, however, appears incorrect to the authors, in spite of its statistical basis.

The prognosis with electroshock on the whole is determined by the choice of case material. Most cases of periodic endogenous or involutional depression respond well or recover with electroshock; it is practically ineffective in chronic schizophrenia, and of doubtful or incomplete value in recent schizophrenia. Many patients in this hospital who showed negative or incomplete response recovered after electroshock treatment.

The therapeutic action of electroshock treatment is certainly not only concerned with the adrenal cortex, but with the total hormone equilibrium, including the thyroid (Reiss, Hemphill, et al. 1951).

The types of response seen most frequently after electroshock, reported here, were different from responses to ACTH. ACTH has so far not appeared to be therapeutically equivalent to electroshock, but as neither the optimum dosage nor the method of application is certain, final pronouncement should be deferred until after fractional ACTH components have been given a trial.

In normals and in chronic stationary psychotic illness, the type of adrenocortical response in different individuals appeared to be fairly constant. Repeated investigations in chronic schizophrenics, made by Pincus, Schenker, Elmadjian, and Hoagland (1949), apparently showed no change, even when alterations in diet had produced increases in plasma ascorbic acid and globulin, and decreases in plasma protein and albumin. Some chronic patients, readmitted to this hospital after a year's interval, have shown the same type of response as they did before their discharge.

Some results of tests for adrenal-cortex responsitivity before and after various treatments

Table 3

No.	Patient	Sex	Age	Diagnosis	Treatment	Weeks between the two tests	Types of Response to				Clinical change between the two tests
							A.C.T.H.		Glucose		
							Before	After	Before	After	
1	M.M.B.	♀	66	Paranoid reaction	E.C.T.	7	1	0	0	0	No improvement
2	A.E.W.	♂	42	Schizophrenia	E.C.T.	12	1	7	0	0	Improved
3	L.E.S.	♀	45	Depression	E.C.T.	4	7	7	0	6	Improved
4	S.V.M.	♂	24	Neurosis	E.C.T.	6	7	6	0	6	Improved
5	G.E.L.	♀	61	Depression	E.C.T.	5	3	7	2	6	Improved
6	A.M.K.	♀	30	Depersonalization	A.C.T.H.	6	7		0	5	Improved
7	P.B.	♂	26	Chronic Schizophrenia	A.C.T.H. and Insulin	36	7	5	7	0	No improvement
8	W.E.C.	♀	52	Depersonalization	A.C.T.H.	10	5	5	3	3	No improvement
9	E.L.D.	♀	36	Depression	Testosterone implant	8	7	7	0	7	Improved
10	L.R.	♀	62	Depression	Testosterone	10	5	7	1	6	Improved
11	I.M.B.	♀	42	Depression	Testosterone	16	1	7	0	3	Improved
12	W.T.R.	♂	17	Schizophrenia	No treatment	6	1	5	0	7	Spontaneous improvement
13	P.H.J.	♂	42	Depression	No treatment	10	1	7	0	0	Spontaneous improvement

are shown in Table 3, and have been selected from a larger series at present under investigation. The first five patients were treated with electroshock. Case 1, who did not improve, did not show any changes in her adrenal-cortex responsitivity, but rather a deterioration in eosinophil response. The other four patients all improved mentally and showed increases in response to either ACTH or glucose or both. Similar correlations were seen in Cases 6 to 11, who were treated with ACTH or testosterone. Of special interest were Cases 13 and 14, in whom spontaneous psychiatric improvement, amounting to recovery, was accompanied by considerable increase in the adrenal-cortex responsitivity.

Although it is too early to establish relationships between adrenocortical responsitivity, and the cause and outcome of psychiatric illnesses, it is reasonable to consider that, where there has been an increase in the adrenocortical responsitivity as the result of treatment, the psychiatric improvement has been to some extent dependent on the improvement in the total hormone equilibrium of the patient. However, assuming that psychiatric improvement is an expression of a more favorable state of brain function, the alteration in adrenal behavior and responsitivity may be due to a functional brain change.

It may even yet appear that in some psychiatric disorders the disturbance of adrenals is the primary cause and most important factor. The experience of the authors gives some support to this suggestion. Successful treatment with adrenal hormones and adrenal-stimulating hormones, in addition to laboratory evidence, will be required to provide confirmation, but therapeutic failure, in the present state of knowledge of adrenal disorders and their treatment, is of little significance.

SUMMARY

1. Adrenal-cortex responsitivity was investigated in 350 psychiatric patients. The results were classified in eight response types.

2. No response types were characteristic of individual disease groups, but there were special features about the distribution of the response types in acute and chronic schizophrenia, and in male anxiety.

3. Disturbances of the responsitivity to injected ACTH were much less frequent, and less severe, than the ability of the pituitary anterior lobe to mobilize ACTH endogenously in response to ingestion of glucose, or after ECT.

4. The distribution of response types shows that different hormonal components may be mobilized respectively by injected ACTH, ingested glucose, or ECT.

5. This provides evidence for the existence of a number of different adrenocorticotrophic fractions with separate functions.

6. Although the response test is not a guide to prognosis, improved responsitivity is sometimes seen after successful treatment with ECT and hormones, and in spontaneous remissions.

7. The significance of the results has been discussed.

RESUMEN

1. La habilidad de responder de la corteza adrenal se investigó en 350 pacientes. Los resultados se clasificaron en ocho tipos de respuesta.

2. Ningún tipo de respuesta demostró ser característico de grupos individuales de enfermedades, pero la distribución de los tipos de respuesta en la esquizofrenia aguda y crónica, y en ansia masculina, revelaron aspectos especiales.

3. Perturbaciones de la habilidad de responder a inyecciones de ACTH fueron mucho menos frecuentes, y menos severas, que la habilidad del lóbulo pituitario anterior de elaborar ACTH endógenamente como respuesta a la ingestión de glucosa, o después de E.C.T.

4. La distribución de los tipos de respuesta demuestra que varios componentes hormonales pueden ser elaborados respectivamente por inyecciones de ACTH, glucosa ingerida, o después de E.C.T.

5. Todo esto suple evidencia a favor de la existencia de varias fracciones adrenocorticotróficas diferentes con funciones separadas.

6. Aunque la prueba de respuestas no constituye un guía en la prognosis, donde la terapia con E.C.T. y hormonas ha tenido éxito, y en remisiones espontáneas, a veces se nota subsiguientemente una mejoría en la habilidad de responder.

7. La importancia de los resultados ha sido discutido.

ZUSAMMENFASSUNG

1. Die Reaktionsfähigkeit der Nebennierenrinde wurde in 350 psychiatrischen Patienten untersucht. Die Resultate wurden acht Reaktionstypen eingeordnet.

2. Kein Reaktionstyp war für bestimmte Krankheitsgruppen charakteristisch, aber gewisse Besonderheiten in der Verteilung der Reaktionstypen in Bezug auf akute und chronische Schizophrenie und Angstzustände in Männern wurden konstatiert.

3. Störungen der Reaktionsfähigkeit gegenüber Einspritzungen von ACTH waren seltener und leichter als die Fähigkeit des Vorderlappens der Hypophysis, ACTH nach der Einnahme von Glukose oder nach Elektroschock endogen zu mobilisieren.

4. Die Verteilung der Reaktionstypen zeigte, dass verschiedene Hormonbestandteile durch eingespritztes ACTH, bezw. eingenommene Glukose oder nach Elektroschock mobilisiert werden können.

5. Hieraus ergab sich Beweismaterial für das Bestehen von verschiedenen adrenocorticotrophischen Fraktionen mit umgrenzten Funktionen.

6. Obwohl die Reaktionsprobe keinen Leitfaden für die Prognose darstellt, wird eine Verbesserung der Reaktionsfähigkeit manchmal nach erfolgreicher Behandlung mit Elektroschock oder Hormonen oder in spontanen Heilungen festgestellt.

7. Die Bedeutung der Resultate wurde besprochen.

RESUME

1. La réaction au cortex surrénal a été étudiée chez 350 sujets psychiatriques. Les résultats observés ont été classés en huit types de réaction.

2. Les types sans réaction étaient caractéristiques des groupes isolés de maladie; toutefois, on a observé des particularités spéciales au sujet de la répartition des types de réaction dans la schizophrénie aiguë ou chronique, ainsi que dans l'anxiété chez les sujets de sexe masculin.

3. Les dérangements de la sensibilité de réaction à l'égard du ACTH injecté ont été beaucoup moins fréquents, et aussi moins prononcés, que l'aptitude du lobe antérieur pituitaire à mobiliser l'ACTH endogènement en réponse à l'ingestion de glucose, ou après l'administration d'E.C.T.

4. La répartition des types de réaction révèle que les divers éléments hormonaux peuvent être mobilisés respectivement par l'ACTH injecté, le glucose ingéré, ou après l'administration d'E.C.T.

5. Ces observations fournissent la preuve de l'existence d'un certain nombre de fractions surréno-corticotrophiques différentes ayant des fonctions distinctes.

6. Bien que l'essai de réaction ne constitue pas un guide en prognose, on note parfois une amélioration de sensibilité de réaction après un traitement efficace par l'E.C.T. et des hormones, et dans les cas de rémission spontanée.

7. La portée résultats observés est examinée.

DISCUSSION

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The experimental efforts of Reiss and his coworkers have added significantly to the data so essential for our ultimate understanding of psychiatric disorders. It is with certain psychiatric interpretations that issue must be taken.

Fundamentally, these investigators, as others before them, have not distinguished sharply enough among a gland's total potential output, its current output, and its reserve. After making the important point that the TRI of "Pincus et al (1949) might mask valuable information," they permit failure to differentiate between adrenocortical current output and reserve to obscure the significance of their own results. In addition, interpretation of their findings suffers when they concentrate their deductions on the adrenocortical-pituitary regulatory system as distinct from the total endocrinium.

As to adrenal cortical output and response, the authors' data may offer some support for the thesis and prediction put forth in 1949 that administration of ACTH and cortisone would produce psychoses in certain predisposed individuals, prepsychotics, and should achieve improvements in areas of psychoneurotic and psychosomatic symptomatology. For example, Reiss and his co-workers report "when some cases of schizophrenia were treated continuously with ACTH . . . cortin and ketosteroid levels remained high for several weeks, indicating a good adrenocortical reaction, but then dropped suddenly and could not be raised in spite of further ACTH treatment. *In these cases there was mental deterioration.*" (The emphasis is the discussant's.) The mental deterioration need not have been the result of a reduced reserve — it could have resulted from the high cortin and ketosteroid levels and/or abrupt shifts in these concentrations which the authors induced.

They further report that in a few patients improvement, either following ECT, sex hormones, or spontaneously, and in one case after ACTH, was accompanied by increased responsitivity to ACTH and glucose. In earlier reports by our group and by others, it has been shown that a rise in eosinophil levels correlates with improvement following sex steroid therapy, insulin and ECT, and also in spontaneous remission. This would bear out the contention raised in previous publications that total absolute potential output of a gland is the sum of current absolute output plus reserve. Thus in the purely hypothetical instance of a fixed absolute potential a low reserve could be related to a high current output and a high reserve to a low output. We have thus seen that high eosinophil levels in clinically improved schizophrenics might point to a lowering in absolute current output of certain

fractions of the cortex and one might then anticipate an increase in reserve. That such may be the case is also indicated by Reiss' data.

Yet, the authors state that "successful treatment with adrenal hormones and adrenal-stimulating hormones, in addition to laboratory evidence, will be required to provide confirmation . . . that in some psychiatric disorders the disturbance of adrenals is the primary cause and most important factor." The implication from the context of the paper suggests that adrenal *deficiency* per se may be at the basis of schizophrenia. This appears, to us, to be controverted by their very own data — and by the frequency with which psychotic disturbances follow ACTH and cortisone therapy. On the other hand, the formulation based on physiologic findings in schizophrenia which predicted the phenomena of a psychotic reaction to ACTH and cortisone in certain individuals has, as we have seen, a considerable body of evidence, including data of the present report, supportive both in respect to proof and counterproof — requirements so essential for biologic experiment.

As to the relationship of the adrenocortical-pituitary regulatory system to the endocrinium, we pointed out (in a discussion of the paper by Hemphill and Reiss) at the First International Congress of Psychiatry in 1950 that the investigators did not sufficiently appreciate the significance of their finding that ECT could stimulate pituitary thyrotrophic production and suggested that the anti-adrenocortical effects of thyroid hormone thus released had to be considered in evaluating the many different physiologic mechanisms through which ECT could exert its beneficial effects. At this time we must stress that any evaluation of the adrenocortical-pituitary system per se could be very misleading when it is not considered in direct context with gonadal, histamine, insulin, and probably parathyroid output or levels, as well as thyroid function. Thus absolute levels of cortical hormones must be differentiated from their operative levels. It may be that even so-called normal, absolute concentrations of adrenocortical hormones may be *operatively* excessive in the presence of deficiency in output of thyroid and/or gonads and/or other endocrine organs. We have considerable supportive evidence on this point.

In conclusion, the data of Reiss et al are most valuable, but some of their psychiatric interpretations must be carefully studied in the light of their own data, of other biologic findings in schizophrenia and other disorders, and in view of the psychopathology being produced by cortisone and ACTH

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The Effect of ACTH, Cortisone, Hydrocortisone and Related Steroids on Mood

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The psychologic effects of ACTH, cortisone and other related substances of the $\triangle^4$ pregnene series were studied as part of a more extensive physiologic investigation of these substances. These observations have been summarized in the reports of Hench, Kendall, Slocumb and Polley,[1,2] Sprague and his associates,[3] and Polley and Mason.[4] This report is an elaboration of the statements made concerning the psychologic changes noted by these and others of our colleagues.

In a preliminary statement,[5] subsequently amplified,[6] we graded the psychologic effects into four general categories. The following is a recapitulation of them:

The responses noted ranged from mild effects reflected primarily in the sphere of mood and affect—grades 1 and 2—to more extensive changes involving the functions of ideation and behavior as well as affect—grade 3. Grade 4, by definition, is composed of alterations in all three of these modalities, of a sufficient degree to meet the diagnostic criteria of a psychotic reaction type.

In the preliminary report of Drs. Hench, Kendall, Slocumb and Polley,[1] they mentioned "the marked sense of well-being" which is experienced. Their impression was that "this euphoria apparently represented not mere relief of pain but a positive factor accompanied by increased mental capacity and activity, sometimes to the point of mild comfortable insomnia." This observation has since been corroborated.[6]

It has been pointed out that sudden or great alterations in the internal environment constitute a stress. Various conforming technics or defenses are set in motion in an effort to minimize the dislocation due to this stress. The resulting process of interaction is adaptation.[7] The psychologic aspect of it is a homologue of the physiologic aspect.

We have construed the observations of the psychologic responses to ACTH and cortisone to be a homologue of the metabolic-physiologic changes which have been described in greater detail.[3] The quantitative nature of these changes, as well as the qualitative variations in the adaptive process they set in operation, is seen most clearly in the case of dislocations of great magnitude. Different levels of adaptedness are direct consequences of changes in the structural order and functional co-ordination.[7] Thus a wide variety of different adaptive mechanisms are mobilized commensurate with the magnitude of the stress.

In the realm of psychologic changes, alterations in mood are most frequently observed and appear first. A great number of physiologic changes induced by these hormones seem to

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be correlated with an elevation of the patient's mood. A diminution of the degree of systemic toxicity, associated with a fall in the usual temperature elevation and a fading in the intensity of local symptoms, is among the most striking. However, this is not necessarily the case in all instances. Indeed, in a number of patients a change in mood seems to presage the systemic physiologic changes.

Then, perhaps in this connection, there is the explicit and implicit psychologic meaning of being treated. There is substantial evidence that the symptomatic efficacy of placebos may be ascribed to this. Although the physiology of gratification as a process is poorly understood, it is generally agreed that the satisfaction of needs serves to dissipate tension.

There is a quantitative factor of importance. On an assumed scale of gratification which ranges from deprivation at one end to satiety at the other end, the closer is the approach to satiety as an upper limit the more effulgent is the elevated mood response. It is in recognition of this quantitative distinction that we have differentiated the grade 2 response from the grade 1 response.

The close relationships between mood, thinking and behavior make artificial any attempt to distinguish effects on one except in the light of equal effects on the others. There are clinical data to support this. Those patients who experience a salutary elevation in mood almost invariably demonstrate commensurate changes in their thinking processes and their behavior.

These patients say they feel stimulated, and they look and act as if they were. Their optimism is paralleled by a sense of physical buoyance. There is a striking change in the content of their dreams and phantasies.

These seem to imply, in a general way, less anxiety and frustration. The activity in the manifest dream content is not as frenetic as it has been in the pretreatment dreams. There is a disappearance of the typical exhausted, anxious feeling on awakening. The patients say they feel less fatigued as a consequence. The retarded, painful, physical restriction, which is the predominant behavior pattern of the sick, yields to a pronounced acceleration of their physical movements. Appetite improves, and the patient voluntarily resumes or increases his participation in social activities.

Not until the intensity of a grade 3 response is reached is there clear-cut evidence that an improvement in the underlying disease and a beneficial response to having dependent needs more adequately satisfied is of minor significance. The impression is gained that either the direct effect of the hormone itself or the changes it provokes in the related metabolic substrate have mobilized a different adaptive mechanism than is used in the functional co-ordination characteristic of the first two grades.

The manifest response of the type we have graded 3 is one of a distinctly psychoneurotic character. In contrast to the responses typical of the first two grades, there is a less apparent relationship between the clinical improvement of the underlying disease and these psychologic symptoms. In fact, sometimes there is an almost inverse relationship; the underlying disease is improved to a considerable degree, yet the patient is depressed, anxious and worried. The grade 3 psychologic response appears to be irrelevant to circumstances in the social environment; there is rarely more than a casual attempt on the part

of the patient to ascribe these symptoms to situational factors. On the other hand, a most striking correlation is seen with those psychologic conflicts which have been characteristic of the patient for many years. In contrast to the dream and phantasy material produced by patients with grades 1 and 2 responses, these patients' dreams are concerned with relatively impotent attempts to resolve conflicts. Immediately on association with this material, conflicts of long standing are recalled. Then, too, the clinical psychiatric symptomatology they present at this time seems to symbolize the same kind of struggle. In addition, it is evident that in many patients these conflicts were managed more effectively up to the time when first the patients were given cortisone or its related substances. The conclusion drawn from this evidence is that these hormones or their related metabolic and dynamic effects have altered ego defenses. This is merely another way of saying that a disruption in the internal environment can be stressful to a degree which compels a new pattern of adaptation.

When these various levels of adaptive response are viewed as components of a larger gestalt, it seems evident that the only psychologic resources or defenses available to grade 3 patients are the uneconomic ones of a psychoneurotic adjustment.

The monistic implications of the etiology of these psychologic responses appear to be corroborated by the data of the grade 4 response. These are psychotic reaction types, the content of which is patently symbolic of conflicts of many years' duration. The delusions, hallucinations and mood variations allude to early psychosexual conflicts and to recent physical symptoms, as well as to a gamut of pertinent interrelationships which seem to be integrated in the paratactic fashion of the psychotic. The response to internal environmental stress in this instance is a primitive, narcissistic adaptation.

The case history of a nurse aged 47 years is prototypically illustrative of some of these points. It is an apposite example of the imprint made by the patient's character organization.

In this particular instance the patient has received a greater number of these agents than has any other patient in our series. On one occasion she was studied in the metabolic unit for a period of 9½ months; on a second occasion this type of study was for 3 months.

During her first hospitalization the patient was given ACTH. A course of cortisone acetate, 100 mg. daily for 18 days and 200 mg. daily for 12 days, was then instituted after a control period of 12 days. Similarly, after a period of 7 weeks during which she was without medication, she was given 200 mg. of cortisone acetate daily concomitantly with 10 mg. of estrone. After another interval of 3 months without medication, a third course of 200 mg. daily of cortisone acetate was given for a period of 18 days in conjunction with testosterone propionate. Δ^5 Pregnenolene and hydrocortisone (compound F) were given on two other occasions. The details of some of these experiences have been reported elsewhere.[2,3,4]

The clinical expression of the psychologic responses the patient evidenced was essentially a caricature of her pretreatment character organization.

The patient is a meticulous, competitive person. The poise and ease she shows on superficial acquaintance with her successfully mask the rather significant burden of tension she carries. She is very exacting of herself even when sick.

The patient's background history suggests the difficulty she had experienced in making

an easy, adequate identification with her mother. In contrast it appears that she has idealized somewhat her warm, friendly relationship with her easy-going father, to whom she was deeply attached. She describes her mother as an extremely prim and exacting woman whose high standards of perfectionism have been a constant challenge to her as well as to her sisters.

The patient was a "better than average" student in primary and secondary schools. After the completion of nursing training, she taught nurses for several years; and since then, as circumstances have permitted, she has been employed as a physician's office nurse.

The patient is well-read, obviously intelligent, poised and attractive, and her daily life in the hospital over a period of many months attested the efficiency and competence with which she discharged her obligations and responsibilities.

The patient described her prepubertal life in significantly vague, general terms; she indicated that menarche was a traumatic experience because of her mother's inhibited attitude toward such matters. She was unprepared for this experience and has suffered since from a moderately severe dysmenorrhea up to age 41 years, when artificial menopause was induced by roentgen therapy.

The patient has been married and divorced twice. On both occasions her husbands drank heavily, and the insecurity and instability their habits imposed on her made it necessary for her to seek an independent domestic adjustment. Both of her husbands are described as easy-going, self-indulgent men. The impression is gained that from the outset neither of these marriages was contracted with any but the most tenuous of ties. The nature and outcome of these marriages seem to suggest the pervasive influence of early nuclear conflicts.

The bearing that the patient's character organization has on her disease as well as on her response to these hormones is seen in the way she epitomizes the effect her arthritis has had on her attitudes and values. She says she has always been a careful, conscientious, fussy person; that she used to worry about things but "since I developed arthritis I just put all of that to one side. I'm much more optimistic, less likely to find fault and am more tolerant."

The patient had a moderately severe rheumatoid arthritis for almost 5 years before this therapy was undertaken. Practically all of her joints except those of the spinal column were affected. In 1945, she was bedridden for 6 months. In 1948, she was moderately disabled. She was awakened frequently at night by pain. She described her morning stiffness as "terrific to have to work off." She had difficulty buttoning her clothes and needed help to get into and out of a tub.

In February, 1948, the patient was given 1,200 mg. of ACTH over a period of 12 days. During the first few days she was apprehensive and anxious. After 11 days she had complete subjective relief from her arthritis. At this time she "felt super," the best she had felt in 5 years. She slept well, her appetite was much improved, and she had a general feeling of well-being.

Promptly on withdrawal of ACTH the patient complained of feeling weepy and exhausted, "nervous and jittery." There were "a lack of pep" and a loss of energy. There were symptoms of tremor, palpitation, thoracic pain and vague paresthesias.

The first course of cortisone consisted of 100 mg. daily for 18 days and 200 mg. daily

for 12 days. Improvement was noted on the third day. There was a definite correlation between the amount of the daily dose and the patient's psychologic responses. The responses included restlessness, tension, inability to plan or concentrate, a sense of mental confusion, difficulty in carrying out specific tasks and shakiness of her handwriting. She complained of a tremendous amount of frustrated energy and was so alert she was unable to sleep. She would arise early in the morning feeling a great surge of energy but by noon would complain of feeling exhausted. Paradoxically, with this feeling of exhaustion she said, "I'm ripping—won't let anyone do anything for me, I'm on the go all the time, thinking things I'd rather be doing."

During the period when the patient's daily dose was 200 mg., she described feeling "a tremendous mental momentum." "Things go round and round in my brain but I haven't the energy to keep pace with it." There was a marked pressure of activity and irritability as a consequence of the drive which, she recognized, exceeded her capacities.

The metabolic balance studies which were carried out and reported by Dr. Sprague and his associates[3] revealed the development of severe hypochloremic, hypokalemic alkalosis similar to that observed in Cushing's disease.

It is of importance to note that although the most marked changes were encountered 12 days after cortisone was withdrawn and were apparently to be attributed to increased absorption, 10 days after cortisone was withdrawn the patient said, "I'm more myself than I've ever been since I've had arthritis. I don't have an irritated brain. I can appreciate things. I'm more intelligent." At that time an electro-encephalogram showed a grade 1 dysrhythmia.

The subsequent two courses of cortisone, which were supplemented with estrone in one instance and with testosterone on the second occasion, were attended by the same grade 3 psychologic response. Sample statements—such as "I'm miles ahead of myself"; "My brain just wheels"; "I feel irritable, I have no pep"—indicate the great effect cortisone has not only on mood but also on behavior and thinking processes. There were evanescent periods of depression with crying, insomnia and much tension. On each of these occasions rounding of the face developed and a slight growth of facial hair resulted. Testoterone seemed to palliate weakness and other side effects to a greater degree than did estrogen.

Before the last cortisone course with testosterone, the patient was given a total of 2.6 gm. of $\triangle^5$ pregnenolene over a period of 10 days. The psychologic response to this steroid was slight. During this time she said she had more energy, and this was reflected in a moderate increase in her activity. While no significant antirheumatic effect was detected,[4] she did evidence an improvement in her subjective sense of well-being. However, this was not at all to be compared with the similar benefits conferred by cortisone and ACTH.

For more than a year after this study lasting 9½ months, the patient received no hormonal therapy until the early part of this year when over a period of 8 weeks she was given 4.2 Gm. of hydrocortisone (compound F).

During the interval between hospitalizations the rheumatoid arthritis was active, but it was not severe until the period immediately before hospitalization.

Shortly after beginning the course of hydrocortisone, the patient was obviously stimulated, said she felt better and was distinctly more active. The response to this agent was

never as pronounced as it had been to ACTH or cortisone. Then, too, she described the effects as being very much slower. Her arthritis improved to the point where, on completion of this course, she said, "I feel better than at any time since I have had arthritis."

Although the intensity of the patient's psychologic reaction was modulated in contrast to her previous experiences, she did have a variety of minor somatic symptoms—dyspnea on slight exertion, dizziness, tightness of her neck, shakiness and tension along with being less fatigued and more able to participate in her usually busy activities.

The definite impression was gained that hydrocortisone increased the patient's affective resilience. There was a perceptibly wider variation in mood. She became more inclined to laugh and also to cry. She seemed more spontaneous. She recognized a facilitated production of her mental stream, and objectively it was apparent in her speech. She was more authoritative, self-assured and positive. At no time did the loss of control which characterized her cortisone therapy appear. These clinical impressions were confirmed by changes in the Rorschach pattern.

In conclusion, it would appear that the nature of the psychologic response which this patient had to the various substances given to her is quite similar to those of a less intense degree typical of grades 1 and 2, as well as to that of the more severe grade 4 response. ACTH, cortisone, hydrocortisone and perhaps to a lesser degree some other chemically related steroids of the $\triangle^4$ pregnene series have the capacity to alter psychologic response. Mood, as well as affect and behavior, reflects this response to an induced stress. The quality of dream content and phantasy is changed.

The form and content of psychologic response is determined significantly by the character pattern of the patient's previous adjustment.

SUMMARY

Psychologic effects of ACTH, cortisone and related substances were graded in four categories, varying from mild changes in mood and affect to psychotic reactions. These reactions are construed as homologues of metabolic-physiologic changes in the internal environment which constitute a stress and set in motion a wide variety of adaptive mechanisms. A detailed case history prototypically illustrates several of the differentiated psychologic response types.

RESUMEN

Los efectos psicológicos de ACTH, cortisone y substancias relacionadas fueron clasificadas en cuatro categorías, variando entre alteraciones menguadas del humor y del efecto, y reacciones psicóticas. Estas reacciones se interpretan como homólogas a cambios metabólico-fisiológicos en el ambiente interno, los cuales constituyen una tensión, y desencadenan una amplia variedad de mecanismos adaptivos. Un caso histórico detallado sirve como prototipo ilustrativo de algunos tipos de respuestas psicológicas diferenciadas.

ZUSAMMENFASSUNG

Die psychologischen Wirkungen von ACTH, Cortison und ähnlichen Substanzen wurden in vier Kategorien eingegliedert, die sich von milden Stimmungs-und Affektänderungen bis zu psychotischen Reaktionen erstrecken. Diese Reaktionen werden als Homologe von metabolisch-physiologischen Aenderungen der inneren Umgebung gedeutet. Derartige Aenderungen stellen einen Spannungszustand (Stress) dar, der eine grosse Anzahl verschiedenartiger Anpassungsmechanismen in Bewegung setzt. Ein des längeren dargestellter Fall gibt ein typisches Bild mehrerer der unterschiedenen psychologischen Reaktionsarten.

RESUME

Les effets psychologiques de l'ACTH, de la cortisone et des substances apparentées sont classés en quatre catégories, allant de changements modérés d'humeur et d'effet jusqu'à des réactions psychotiques. Ces réactions sont interprétées comme étant des homologues des changements métaboliques-physiologiques du milieu interne qui constituent une tension et mettent en oeuvre une grande variété de mécanismes adaptifs. Un cas d'observation détaillé illustre à titre prototypique plusieurs des types de réaction psychologiques différentiée.

DISCUSSION

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The appearance of psychologic changes and psychotic reactions with the administration of ACTH and cortisone provides a new and challenging approach to psychiatric understanding.

This significant report records some opinions and interpretations of observers who have had a unique association with the development of therapy for the cortagen diseases, and their statements will doubtless be widely accepted. It has been repeatedly shown in the history of science in general and, for our purposes, medicine in particular, that disagreement concerns interpretation more often than findings. No sensible person can question the validity of Rome's and Braceland's observations, but it is fair to ask that these should be so recorded that others can do their own thinking from the data. From this paper, excellent in many other respects, one can gain no idea of the incidence of the four described responses in proportion to the number of cases treated nor of the time of development of the psychologic signs in relation to the institution of the therapy. This type of information would be valuable to other workers, as would greater detail of the basic personality pattern of the cases, showing the different types of psychologic response. If this type of data is or will be available elsewhere, it would be helpful if the authors said so.

With respect to the use of the words *stress* and *adaptation*, the writer feels that these have in the past embodied useful ideas. Now, however, they need re-examining as they are tending to become catch words and concepts that obscure the necessity for more profound thinking. This danger is illustrated in the authors' statement which says of the action of the hormones that "a disruption in the internal environment can be stressful to a degree which compels a new pattern of adaptation." Are there not other and simpler ways of expressing this thought and at the same time underlining our ignorance?

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In view of current findings of the psychologic and psychiatric effects of cortisone and ACTH, this communication is of particular importance. Considerable interest in the relationship of the endocrines to psychiatric disturbances was evidenced by Kraepelin, Freud, and by such recent investigators into physiologic psychiatry as Hoskins, Altschule, and the Sacklers. The latter group put forth a neuro-endocrine theory predicting some of these findings on the basis of biologic and therapeutic experimentation whose data pointed to an endocrine involvement in the etiology and pathogenesis of schizophrenia. Psychiatry, nonetheless, had to wait further evidence. This support may now be provided through the current studies on the cerebral effects of cortisone and ACTH.

The authors' definition of psychotic reaction types can be very helpful. It would seem that it is of particular importance to differentiate between (1) the reactive and realistically-based psychologic improvement secondary to alleviation of somatic complaints; and (2) the euphoria which may be the first evidence of a deleterious effect of pituitary and adrenocortical hormones upon cerebral function. In respect to consideration of grade 3 response, the implication that it may be a psychoneurotic type of reaction and that grade 4 may be a psychotic type of reaction would suggest that the authors might consider the latter process as an extension of the former. There are some authors who consider these processes to be biologically antithetical.

Investigation of the psychic influences of physiologic substances which are normally involved in metabolic functions should contribute vastly to our understanding of the pathophysiology of psychiatric disorders.

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The Mathematics of the Unconscious

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There seems to be no evidence that psychoanalysis, in its pursuit of determinism, turns its back finally on factors of coincidence. Not without reason, however, analysis regards coincidence—especially in its popular aspects—with suspicion, because "coincidence" often serves as a behavioristic tag to disguise causes and motives that are determinable through examination of the deep levels of the psychic mechanism. Analysis prefers to set limits on its credence.

If I write the first five-figure number that comes to my mind, say, 43,821, and then check with another five-figure number that I wrote down six months ago—which, for the sake of example, turns out to be 38,412—it is a coincidence in the popular sense that these two chance numbers should contain the same digits. It is also a coincidence if the next bus ticket I buy bears the number 43,821. Whereas the analyst would support the popular verdict in the second case, he would feel that coincidence should be ruled out in the first case. Selection of the numbers I have written down has been unconsciously determined by me. The analyst would set himself to examine that determinism by inquiring into my associations. He would draw assurance for his attitude from Freud's comments on chance numbers in his *Psychopathology of Everyday Life*. Freud says: "I know of no other individual observation which would so readily demonstrate the existence of highly organized thinking processes, of which consciousness has no knowledge."

Case A: I offer these comments to introduce some rather unusual "coincidences" which I noted when reading Freud's paper on "A Neurosis of Demoniacal Possession in the 17th Century" (1923: *Collected Papers*, Volume 4). This paper tells the story of Christoph Haitzmann, a painter who died in 1700. In August 1677, Haitzmann suffered convulsive seizures and visions which led him to seek the help of the Church. He was asked whether he had any "illicit traffic with the Evil One." On this point Freud writes: "Whereupon he confessed that nine years previously, in a state of despondency in regard to his art and of despair about his livelihood, he had succumbed to the nine-times-repeated temptation of the Evil One and had given his bond in writing to belong to the Devil body and soul at the end of nine years." The contract was due to expire on September 24, 1677. Haitzmann was convinced that only the Virgin could aid him and force the Devil to disgorge the bond, which had been written in blood. According to Church records, the painter embarked on a period of expiation and prayer which resulted in the Devil's appearing before him in a Holy Shrine and handing over the bond. Thereafter Haitzmann's visions and seizures ceased—but only for a time. In May 1678, he again sought Church aid. This time he revealed that, although he had made no earlier mention of it, he had contracted a prior bond

with the Devil. This bond had been drawn up in ink. He believed that his new seizures were due to the Devil's continued possession of this bond. After more prayer, the Ink Bond was returned to him on May 9, 1678, at nine o'clock in the evening.

These two bonds were placed in the hands of the Church. Copies of them are reproduced by Freud. Both bonds bear the date 1669.

I shall reserve until a little later a summary of Freud's deductions on Haitzmann's illness, because, as will be seen in due course, the "coincidences" about to be examined are closely related to those deductions. In passing, it should be observed that Freud did not point out the existence of these "coincidences" in his essay.

(a) To begin with, Haitzmann lays stress on the figure nine. The Blood Bond is of nine years' duration and was contracted in response to a nine-times-repeated temptation. It is due to expire on September 24, 1677. We commonly write such dates in the following form:

24/9/1677

Let us experimentally add these figures in the following way:

$2 + 4/ + 9/ + 1 + 6 + 7 + 7 = 36$

To reduce this sum to a single digit let us add again:

$3 + 6 = 9$

A coincidence? We could scarcely assert, at this stage, that it was much more. But let us proceed.

(b) If, as Haitzmann claimed, the Blood Bond was due to expire on September 24, 1677, and was of nine years' duration, it should have been drawn up—as Freud points out—on September 24, 1668, not in 1669, as the records suggest. Following the previous method let us add again:

24/9/1668

$2 + 4 / + 9 / + 1 + 6 + 6 + 8 = 36$

$3 + 6 = 9$

Another coincidence? Obviously there is no reason to become too credulous. Again, let us proceed.

(c) According to the records, the Ink Bond was delivered up by the Devil on May 9, 1678. Another sum:

9/5/1678

$9 / + 5 / + 1 + 6 + 7 + 8 = 36$

$3 + 6 = 9$

We may now suspect that the element of coincidence is beginning to vanish in face of an unexpected motif, especially when we note that the Ink Bond was specifically delivered up at *nine* o'clock in the evening.

(d) We have already seen in (b) that Haitzmann's sense of time must have been astray in regard to the Blood Bond, because it should have been signed in 1668, not in 1669, to make the termination of the contract so important to him. With the Ink Bond, however, we can see that the nine-year interval would have allowed it to be signed in 1669. In fact, it should have been signed on May 9, 1669. Let us add again:

9/5/1669
9 / + 5 / + 1 + 6 + 6 + 9 = 36
3 + 6 = 9

(e) In the details of Haitzmann's life given above no mention was made of a diary which he kept for a period after he had successfully induced the Devil to hand back the Blood Bond. Freud notes of this diary: "The entries date back from his successful redemption until January 13 of the following year, 1678." On that date, Haitzmann suffered new convulsions and visions. The date was obviously significant to him. Let us add:

13/1/1678
1 + 3 / + 1 / + 1 + 6 + 7 + 8 = 27
2 + 7 = 9

Whether these results are coincidental or not, they bear a strange relevance to what Freud had to say about the theme of Haitzmann's obsessional delusions. He draws attention to the obvious importance of the number nine in Haitzmann's fantasies—the duration of the bond, the nine-times-repeated temptation—and he goes on:

"The number nine has become familiar to us in neurotic fantasies. Nine is the term of the months of gestation, and reference to the number nine, whatever its connection, directs our attention to a fantasy of pregnancy. In this case, to be sure, the number refers to years, not to months, and it might be objected that the number can be of significance in other directions. But who can say whether much of the sacrosanctity of this number is not altogether due to its relation to pregnancy? The change from nine months to nine years need not throw dust in our eyes. Dreams have taught us how 'unconscious mental activity' plays with numbers. If, for example, the number five occurs in a dream, this refers invariably to a five of significance in waking life; the five may refer, however, in reality to five years' difference in age or to a company of five people, and this will appear in the dream as five pieces of money or five pieces of fruit. That is to say, the number itself is retained, but the denominator is changed in accordance with the demands of condensation and displacement. Nine years in a dream could easily represent nine months in reality. The numbers of waking life are played with by the dream-work in other ways, too, as when the latter shows a lordly disregard for ciphers, not treating them as numbers at all. Five dollars in a dream may stand for fifty, five hundred, five thousand of the dollars of reality."

With these observations in mind, the strange recurrence of the number nine in the sums above may give a new, if somewhat perplexing insight into the activities of the Unconscious. The five examples suggest that more than coincidence is involved, especially when we find Freud deducing from the evidence he himself selected that Haitzmann was suffering from a homosexual fixation on his father, that the delusions were precipitated by his father's death, that his fantasies were concerned, in part at least, with an unconscious desire to bear a child (i.e., in nine months) to his father, and that the bonds in blood and ink were fortuitous inventions to gain him the help and protection of the Church. Freud suggests that the blunders which Haitzmann made in the dates of the bonds—notably that they were both allegedly drawn up in 1669 for a period of nine years, but were redeemed at

dates which made it impossible for this to be true in both cases—"may be regarded as a piece of unintentional honesty; it enables us to guess that the alleged earlier pact (in ink) was actually fabricated at a later date." I would suggest that the "unintentional honesty" goes even beyond this, if any value can be placed upon the unexpected results of the arithmetic above. What these results seem to amount to is this: They are repeated declarations of an unconscious fixation on the number nine and hence on the pregnancy fantasy. They might possibly serve as a guide in themselves; they are certainly valuable from a corroborative viewpoint.

How the Unconscious could perform these mathematical computations with such accuracy—bearing in mind that they involve human actions on certain dates and not merely paper arithmetic—we certainly do not yet understand, and perhaps we should not expect an automatic understanding. The important factor is the empirical evidence to be drawn from these (superficially quite arbitrarily selected) dates.

Case B: In a recent issue of the *Psychoanalytic Quarterly* (20:2, 1951) William N. Evans discusses a case of "Simulated Pregnancy in a Male," in the course of which brief reference is made to a feat of unconscious arithmetic that was recorded during treatment of a homosexual. As the title of the paper suggests, this young man had something in common with Haitzmann; during treatment he worked through a clearcut pregnancy fantasy.

To summarize the analyst's report: On November 3, the patient announced that the end of the treatment would be reached two days later, November 5, which was his mother's birthday. On November 4 he said: "You can't hurry these things; nature must take its course." The analyst then pointed out to him that treatment had begun on January 29 and asked whether the phrase "two hundred and eighty days" conveyed anything to him. To quote: "He recalled his mother's anxious concern about the matter of dates during her last pregnancy, but nothing more. Having consulted a calendar prior to the session, I pointed out that if he were to count the days from January 29, the 280th day was, in fact, the date he had chosen, the 5th of November."

From the evidence to be drawn from these two cases it would appear that, at least in certain instances, the unconscious reveals a remarkable flair for mathematical precision.

Before continuing to investigate other examples that may help to throw some light on this matter, I want to refer briefly to an interesting principle of arithmetic which, as far as I know, has no place in the teaching and practice of orthodox mathematics.

When dealing with Haitzmann's dates, I did not point out that examples (b) and (d) follow inevitably from (a) and (c) for the simple reason that the dates concerned cover nine-year intervals. This may seem strange to some readers, but is easily demonstrated.

In terms of addition which is reduced to a single digit, nine and multiples of nine always add up to nine. Thus:

$9 \times 6 = 54 : 5 + 4 = 9$
$9 \times 9 = 81 : 8 + 1 = 9$

Alternatively:

$81 - 9 = 72 : 7 + 2 = 9$
$27 - 9 = 18 : 1 + 8 = 9$

This characteristic of constancy is transferred to other figures if (and if only) nine or multiples of nine are introduced. Thus, if we take the figure 62 and add the 6 and the 2 the resulting sum is 8. Now let us see the effect of nine on this result:

$$62 - 9 = 53 : 5 + 3 = 8$$
$$62 + 9 = 71 : 7 + 1 = 8$$
$$62 - 27 = 35 : 3 + 5 = 8$$

With this in mind, it will be seen that examples (b) and (d) follow automatically from (a) and (c), simply because the Blood and Ink Bonds are purported to have been drawn up to cover periods of nine years. At a later stage there will be other observations to make on this.

Case C: In the meantime I should like to offer an illustration that not only concerns this point, but adds something to the earlier material. In the *International Journal of Psycho-Analysis* (2:314-315, 1921), Owen Berkeley-Hill had some figures to offer in the course of a paper on "The Anal-Erotic Factor in the Religion, Philosophy and Character of the Hindus." He referred to the Brahman belief that at the end of vast periods of time called "days of Brahma," each lasting 4,320,000 years, the whole universe is reabsorbed and, after remaining dormant for equally long periods, is again evolved. No great imagination is needed to see this as part of a birth fantasy, but the figures would seem to indicate that this is a fantasy on a monumental scale. For example, according to Berkeley-Hill a "day of Brahma" and its associated intervals are divided thus:

The Krita-Yuga	1,728,000	years
The Treta-Yuga	1,296,000	"
The Dvapara-Yuga	864,000	"
The Kali-Yuga	432,000	"
A Mahayuga	4,320,000	"
	× 71	
A Manu period	306,720,000	"
	× 14	
	4,294,080,000	"
With 15 intervals of 1,728,000 years each	25,920,000	"
	4,320,000,000	"

I have given these figures just as listed by Berkeley-Hill and do not pretend to understand the significance of the various additions and multiplications. However, another form of significance becomes evident when these so-called time-periods are subjected to addition and reduction to a single digit. Dealt with seriatim, they are:

1,728,000	when	added	= 18 : 1 + 8 = 9
1,296,000	"	"	= 18 : 1 + 8 = 9
864,000	"	"	= 18 : 1 + 8 = 9
432,000	"	"	= 9
4,320,000	"	"	= 9
× 71			
306,720,000	"	"	= 18 : 1 + 8 = 9
× 14			
4,294,080,000	"	"	= 27 : 2 + 7 = 9
25,920,000	"	"	= 18 : 1 + 8 = 9
4,320,000,000	"	"	= 9

In short, we find what can scarcely be interpreted as anything other than a persistently repeated (actually, a nine-times repeated) reference to the nine months' gestation period. As I noted above, I have no idea what the multiples 71, 14, and 15 signify, but their presence makes no difference to the result. No matter what figure or group of figures is used for multiplying 9, the answer when reduced by addition to a single digit will always be 9.

Since, however, many people will certainly feel disinclined to attach much significance to the "coincidences" listed above—at least to the extent of making any general deduction therefrom—it may be worth an effort to examine some other examples. All of the examples that follow in the next section are taken from Freud's writings and should be accessible to most readers for personal reference.

Case D: In his *Psychopathology of Everyday Life,* Freud offers a group of analyses of "chance numbers." One of these was supplied to him by Alfred Adler, and, we may feel, was from Adler's personal experience rather than, as is suggested, from a third person. The report of this example begins: "Last night I devoted myself to the *Psychopathology of Everyday Life* and I would have read it through had I not been hindered by a remarkable coincidence. When I read that every number that we apparently conjure up quite arbitrarily in our consciousness has a definite meaning, I decided to test it. The number 1734 occurred to my mind. The following associations then came up: $1734 \div 17 = 102$; $102 \div 17 = 6$."

Adler's report then pursues associations to these numbers, during which the number six is revealed as a reference to Mullner's book *Schuld* (Fault)*—the sixth volume of the Reclam Universal Library. The inquiry then proceeds along lines that take us away from the present theme.

Let us pursue the method of simple addition in application to this "chance number," 1734:

*The German word *Schuld* is probably more often translated as meaning "guilt." However, it is translated as "fault" in *The Basic Writings of Sigmund Freud* (New York, Modern Library, 1938), p. 153, and I quote it here from that context.

$$1 + 7 + 3 + 4 = 15$$
$$1 + 5 = 6$$

It will be noted that this is the result at which the person who selected the number also arrived—by a different route. In short, if it emerges that any value is to be set on this method of inspecting chance numbers, independent corroboration of the person's associations has been found. We note that the number six was associated with a book entitled *Schuld* (Fault). The original statement said that the person desired to test Freud's view on chance numbers. In short, he wished to prove to himself whether they were right—or, perhaps more significantly, to prove whether they were wrong. If, as there may be reason to suspect, the person was Adler himself, we will know from his subsequent split with Freud that he would wish to prove Freud wrong. He would wish to show that Freud was committing a fault, sin, or crime against mankind by stressing the activities of the Unconscious, and he would feel guilt because of this wish. The opposing tendencies meet in the word *Schuld*. True, the split between Adler and Freud did not come until much later, but perhaps here was a first hint of it. It is unlikely that Freud missed it.

Case E: Here is Freud giving a case from his own experience: "In a letter to a friend, I informed him that I had finished reading the proof sheets of *The Interpretation of Dreams*, and that I did not intend to make any further changes in it, 'even if it contained 2,467 mistakes.' I immediately attempted to explain to myself the number and added this little analysis as a postscript to the letter. It will be best to quote it now as I wrote it when I caught myself in this transaction: 'I will add hastily another contribution to the *Psychopathology of Everyday Life*. You will find in the letter the number 2,467 as a jocose and arbitrary estimation of the number of errors that may be found in the dream-book. I meant to write: no matter how large the number might be, and this one presented itself . . .' Freud proceeds with his associations and gives a satisfying answer, but I feel there is something else to be said. Let us add his number 2,467:

$$2 + 4 + 6 + 7 = 19$$
$$1 + 9 = 10$$
$$1 + 0 = 1$$

In the last sentence quoted above Freud wrote: "I meant to write: no matter how large the number might be, and this *one* presented itself." Do we not suspect that Freud "meant" to write: "I do not intend to change my book, even if it contains a (one or a single) mistake"?

A valueless example? Well, perhaps, but then little more is claimed for this approach than that it may give some better insight into the mathematical activities of the Unconscious. Let us rather continue.

Case F: Freud writes in his *Psychopathology of Everyday Life*: "One day, it struck one of my patients that he was particularly fond of saying: 'I have already told you this from 17 to 36 times.' And he asked himself whether there was any motive for it. It soon occurred to him that he was born on the 27th day of the month, and that his younger brother was born on the 26th day of another month, and he had ground for complaint that fate had

robbed him of so many of the benefits of life, only to bestow them on his younger brother. Thus he represented this partiality of fate by deducting 10 from the date of his birth and adding it to the date of his brother's birthday. "I am the elder and yet am so 'cut short.'"

Here we note that Freud added 10 to one number and deducted 10 from another number. In short, here is an apparently arbitrary act for which no justification is offered except that the answer is persuasively satisfying. What if we can show that the result is implicit in the original figures without any such manipulation? Let us add the digits in the birthday dates:

(Patient) $27 : 2 + 7 = 9$
(Brother) $26 : 2 + 6 = 8$

Now let us follow the same process with the original figures from which the patient associated to this matter of birthdays (as distinct from the deductions made therefrom):

$$36 : 3 + 6 = 9$$
$$17 : 1 + 7 = 8$$

Once again, we find that these additions corroborate the associations.

Case G: Here is another example, this time from Freud's *The Interpretation of Dreams:* "A man dreams: He is sitting in the B's house (the B's are a family with which he was formerly acquainted), and he says: 'It was nonsense that you didn't give me Amy for my wife.' Thereupon he asks the girl: 'How old are you?' Answer: 'I was born in 1882.' 'Ah, then you are 28 years old.'"

In examining this dream, Freud notes at the outset: "Since the dream was dreamed in the year 1898, this is obviously bad arithmetic, and the inability of the dreamer to calculate may, if it cannot be otherwise explained, be likened to that of a general paralytic." Freud's verdict, then, is "bad arithmetic." But is it? Let us add:

(Born in) 1882

$$1 + 8 + 8 + 2 = 19$$
$$1 + 9 = 10$$
$$1 + 0 = 1$$

(Age) 28

$$2 + 8 = 10$$
$$1 + 0 = 1$$

From the point of view pursued here anyway, this arithmetic is anything but "bad." Of course, if we are again faced with the challenge of "coincidence!" we have at our disposal no more resources than for the curious results of Haitzmann's dates. We cannot show the mechanics of Unconscious arithmetic; we can only show the products of the additions and trust that the consistency with which accurate answers are offered will rule out "coincidence."

Case H: This is another example from Freud's *Psychopathology of Everyday Life.* He tells of a patient who "let the number 426,718 come to his mind." Freud then tells of the patient's associations. "First came a joke he had heard: 'If your catarrh of the nose is treated by a doctor, it lasts 42 days; if it is not treated, it lasts—six weeks.'" Freud elucidates: "This corresponds to the first digit of the number ($42 = 6 \times 7$)."

I will quote the remainder of the report, reserving comment until later: "During the blocking that followed this first solution, I called his attention to the fact that the number of six digits selected by him contains all the first numbers except 3 and 5. He at once found the continuation of the solution: 'We were altogether 7 children; I was the youngest. Number 3 in the order of the children corresponds to my sister A., and 5 to my brother L.; both of them were my enemies. As a child I used to pray to the Lord every night that He should take out of my life these two tormenting spirits. It seems to me that I have fulfilled for myself this wish: "3" and "5," the *evil* brother and the *hated* sister, are omitted.' 'If the number stands for your sisters and brothers, what significance is there to the 18 at the end? You were altogether only 7.' 'I often thought if my father had lived longer, I should not have been the youngest child. If one more would have come, we should have been 8, and there would have been a younger child, toward whom I could have played the role of the older one.' "

First, we will note an error in Freud's statement. In addition to the absence of the numbers 3 and 5, the number 9 is also missing. The patient is not asked to explain this. Second, we note that, in the last sentence of the quotation, the word "one" occurs twice.

Now let us add the number 426,718:

$$4 + 2 + 6 + 7 + 1 + 8 = 28$$
$$2 + 8 = 10$$
$$1 + 0 = 1$$

It will be noted that this product and its relation to a verbal context is similar to the example in which Freud declared that he would not alter what he had written.

I have introduced this example here because it surely entitles us to ask whether the arbitrary omission from consideration of a digit not included in a "chance number" is justified—especially when close attention is paid to other omitted digits. Three digits are omitted from the number 426,718, yet Freud reserved consideration for 3 and 5. Whether he did this intentionally or not we do not know, but on the evidence it is scarcely possible to regard the omission as any less arbitrary than his addition and subtraction of 10 in another case quoted above and his tag "bad arithmetic" applied to still another case. The evidence offered to date does not suggest that the Unconscious indulges in arbitrary tricks.

Case 3: It is with the aim of showing that the Unconscious is just as reliable as the Conscious in solving mathematical problems (although its method is different) that I offer the next example, which is also from Freud. It is, in fact, a continuation of the example supplied to Freud by Adler. According to Adler's report, the man who thought of the chance number 1734 wished to resolve to his own satisfaction how the number 17 came to be involved in the problem.

To quote: "My wife, whom I awakened through my getting up at night . . . said that nothing came to her mind when she thought of a number. I answered 'Let us try it.' She named the number 117. To this I immediately replied, '17 refers to what I just told you (a reference to Shakespeare's *Macbeth*), furthermore, I told you yesterday that if a wife is in the 82nd year and the husband is in the 35th year, it must be a gross misunderstand-

ing.' For the last few days I have been teasing my wife by maintaining that she was a little old mother of 82 years. $82 + 35 = 117$."

Let us use our method:

a. (82nd year): $82 : 8 + 2 = 10$

$1 + 0 = 1$

b. (35th year): $35 : 3 + 5 = 8$

c. The sum of these two products: $1 + 8 = 9$

d. The number named by the man's wife is 117:

$1 + 1 + 7 = 9.$

So, the woman's "chance number" and the husband's fantasy on ages are twice equated, first through orthodox (Ego) mathematics and second through what is here postulated as the unorthodox, but seemingly highly conventional mathematics of the Id.

It may surprise some readers to know that this finding is universally valid. As a test case let us take two "chance numbers," say 364 and 28, and proceed according to what is described above as (1) Ego and (2) Id arithmetic.

(1)		(2)		
	364		$3 + 6 + 4 = 13$	$: 1 + 3 = 4$
	28		$2 + 8 = 10$	$: 1 + 0 = 1$
	392		$3 + 9 + 2 = 14$	$: 1 + 4 = 5$

So, from two approaches, we find that the "chance numbers" add up to a common result, 5. By "common," of course, is implied a concession to the process of addition through reduction to a single digit. But there is something more than this: The figures in the "chance numbers" can be rearranged in any way and the reduction will be identical with that shown above. Thus, let us reshuffle the figures 364 to 436 and reverse the figures 28 to 82:

(1)		(2)		
	436		$4 + 3 + 6 = 13$	$: 1 + 3 = 4$
	82		$8 + 2 = 10$	$: 1 + 0 = 1$
	518		$5 + 1 + 8 = 14$	$: 1 + 4 = 5$

Now, we see where the great divergence between Ego arithmetic and Id arithmetic comes in. In (1) the rearrangement of figures produces an entirely different result, but in (2) the result remains constant. In short, Id arithmetic is much more conventional than Ego arithmetic.

Case J: With this in mind, I believe we can confidently examine some cases from Freud where "chance numbers" would superficially belie the general thesis of this paper. In his *Psychopathology of Everyday Life*, he quotes an example given by Jones. An acquaintance of Jones let the number 986 come into his mind. "Six years ago, on the hottest day he could remember, he had seen a joke in an evening newspaper, which stated that the thermometer had stood at 986° F., evidently an exaggeration of 98.6° F. We were at the time seated in front of a very hot fire, from which he had just drawn back, and he remarked, probably quite correctly, that the heat had aroused his dormant memory."

How do we relate our approach to this? First it is noted that the numbers have not been

changed, although the Ego mathematician will see a great difference between 986 and 98.6. By simple addition, of course, we know that $9 + 8 + 6 = 9 + 8 + 6$. The point involved is one that Freud has observed in his comment, quoted earlier, that the dream-work "shows a lordly disregard for ciphers." That view is taken for granted by psychoanalysts, but a reason for it can now be offered that is entirely consonant with this approach to the problem of Unconscious mathematics. I shall return to this a little later.

Cases K and £: In *The Interpretation of Dreams* Freud details a woman patient's dream: "She wants to pay for something or other; her daughter takes 3 florins 65 kreuzer from her purse; but the mother says: 'What are you doing? It costs only 21 kreuzer.'" Freud's analysis: "This fragment of the dream was intelligible without further explanation owing to my knowledge of the dreamer's circumstances. The lady was a foreigner, who had placed her daughter at school in Vienna, and was able to continue my treatment as long as her daughter remained in the city. In three weeks the daughter's scholastic year would end, and the treatment would then stop. On the day before the dream, the principal of the school had asked her whether she could not decide to leave the child at school for another year. She had then obviously reflected that in this case she would be able to continue the treatment for another year. Now, this is what the dream refers to, for a year is equal to 365 days; the three weeks remaining before the end of the scholastic year, and of the treatment, are equivalent to 21 days (though not to so many hours of treatment). The numerals, which in the dream-thoughts refer to periods of time, are given money values in the dream, and simultaneously a deeper meaning finds expression—for '*time is money*'; 365 kreuzer, of course, are 3 crowns 65 kreuzer. The smallness of the sums which appear in the dream is a self-evident wishfulfillment; the wish has reduced both the cost of the treatment and the year's school fees."

Here again it can be seen how indifferent the Unconscious is to ciphers, for 365 (days) = 300 (kreuzer) + 65 (kreuzer) and also = 3 (crowns) + 65 (kreuzer). Freud gives a similar example in which a dreamer converts a gift of 150 florins into 1 florin 50 kreuzer. However, the idea of "lordly disregard" does not give a true picture of the economy of the Unconscious, which appears to follow a completely rigid pattern. Thus, in the first example:

(Days) $365 : 3 + 6 + 5 = 14 : 1 + 4 = 5$
(Kreuzer) $3 + 0 + 0 \;/\; + 6 + 5 = 14 : 1 + 4 = 5$
(Crowns, kreuzer) $3 \;/\; + 6 + 5 = 14 : 1 + 4 = 5.$

And, in the second example:

(Crowns) $1 + 5 + 0 = 6$
(Crowns, kreuzer) $1 \;/\; + 5 + 0 = 6$

* * *

A little earlier an example was examined in which figures were reshuffled without changing the result in terms of what may be the mathematical method of the Unconscious. I would like to take this farther, to show that there are no loopholes in the method. Let us take two new "chance numbers"—37,231 and 927—and proceed. In doing so, however,

let us make the setting out of our arithmetical problems easier by using the sign Σ. Thus, Σ91,377 = 27; Σ27 = 9.

We will follow the two courses of Ego and Id arithmetic in dealing with the "chance numbers" given above:

a. Σ37,231 = 16; Σ16 = 7
b. Σ927 = 18; Σ18 = 9

Σ16 = 7

c. Σ38,158 = 25; Σ25 = 7

The "reduced" results are shown to be identical. Now, let us carry the reshuffling process beyond the earlier stage, not only rearranging the digits in each of the "chance numbers," but interchanging the digits between the numbers. For example, the figures 7 and 9 are put in the top line and the figures 2 and 3 in the bottom line. Thus:

a. Σ91,737 = 27; Σ27 = 9
b. Σ223 = 7

Σ16 = 7

c. Σ91,960 = 25; Σ25 = 7

Let us now make our problem a little more involved by selecting five "chance numbers" in which there are several ciphers:

Σ29,943 = 27; Σ27 = 9
Σ1,001 = 2
Σ19 = 10; Σ10 = 1
Σ323 = 8
Σ100 = 1

Σ21 = 3

Σ31,386 = 21; Σ21 = 3

We can now show that omission of the ciphers make no difference at all to the result:

Σ29,943 = 27; Σ27 = 9
Σ11 = 2
Σ19 = 10; Σ10 = 1
Σ323 = 8
1 = 1

Σ21 = 3

Σ30,297 = 21; Σ21 = 3

Alternatively, it can be shown that, in accordance with this method, intrusion of ciphers at any place in the numbers does not disturb the Id result:

$$\begin{aligned}
\Sigma 20{,}909{,}403 &= 27;\ \Sigma 27 = 9\\
\Sigma 1{,}001 &= 2\\
\Sigma 190 &= 10;\ \Sigma 10 = 1\\
\Sigma 300{,}023 &= 8\\
\Sigma 100 &= 1\\
&\overline{\qquad}\\
&\Sigma 21 = 3
\end{aligned}$$

$$\overline{\qquad\qquad}$$

$$\Sigma 21{,}210{,}717 = 21;\ \Sigma 21 = 3$$

As a final example of the remarkable consistency of this approach, let us break up the "chance numbers" in a different way, say, into six pairs and a single figure. Thus:

$$\begin{aligned}
\Sigma 29 &= 11;\ \Sigma 11 = 2\\
\Sigma 94 &= 13;\ \Sigma 13 = 4\\
\Sigma 31 &= 4\\
\Sigma 11 &= 2\\
\Sigma 93 &= 12;\ \Sigma 12 = 3\\
\Sigma 23 &= 5\\
1 &= 1\\
&\overline{\qquad}\\
&\Sigma 21 = 3
\end{aligned}$$

$$\overline{\qquad}$$

$$\Sigma 282 = 12;\ \Sigma 12 = 3$$

In short, no matter how the numbers are arranged—or how they are "disintegrated"—a simple addition of them gives an identical reduction. Moreover, this reduction is identical with the simple addition of the digits in all the Ego results.

I am afraid that I have gone into somewhat tedious detail in this inquiry, but the reason is clear. If, by good fortune, some light has been thrown upon the mathematical processes of the Unconscious, it allows us to understand why the Unconscious cares nothing for the order in which "chance numbers" occur, how it could be possible that any type of figure (dates, temperatures, money, etc.) could be subject to displacement, and how the Unconscious can produce results—as we have seen with Haitzmann—which seems to go somewhat beyond the commonly-accepted limits of coincidence.

* * *

At this stage, some examples from my personal experience may be in order. I believe they serve to illustrate what may be a practical method of using some of the findings in this paper.

First, an example that occurred in writing.

Case M: Person D wrote to me: "I can never manage my finances properly. I find I'm £3.8.1 out in my budget, but I suppose if I had an adding machine I might make errors,

too—perhaps £7,743,219,834,765 at a time, although I suppose it would amount to the same thing since I haven't much money anyway."

Let us examine the two sums of money mentioned:

(a) £3.8.1

$3 + 8 + 1 = 12;\ 1 + 2 = 3$

(b) £7,743,219,834,765

$= 66;\ \Sigma 66 = 12;\ 1 + 2 = 3$

In the original quotation, the sentence "I suppose it would amount to the same thing" seemed something of a non sequitur. The two reduced totals suggest something different.

Here, of course, we are back to the issue of how often a coincidence must occur before it can be accepted as scientific evidence. With this in mind, I offer what I have fondly come to regard as The Case of the Barking Dog, which should give the incredulous something to get their teeth into.

Case N: In the course of talking, Person J produced the chance number 941,345. No sooner had he done so than I noted that a dog was barking in the distance across the park outside. J must have noted this, too, because his ensuing associations which I had requested were: *dog, canine, teeth, ate.* That was all. His excuse for not continuing was: "There doesn't seem anything more to say."

I immediately subjected the chance number to simple addition:

$\Sigma 941{,}345 = 26;\ 2 + 6 = 8$

I was then struck by the fact that the word *ate* (which he had pronounced as *ayt,* not as *ett,* which is the "approved" British pronunciation) was a homonym for *eight.* In short, his observation that there was "nothing more to say" seemed to have some element of psychic honesty about it. At this stage, another intriguing point emerged. There were only four words in his original associations—*dog* (containing three letters), *canine* (six letters), *teeth* (five letters) and *ate* (three letters). By simple addition:

$3 + 6 + 5 + 3 = 17;\ 1 + 7 = 8$

It seems to me that here is a type of coincidence that is slightly stupefying in its complexity, not only because of the speculations it may provoke on a mathematical plane, but also because of the circumstance noted at the time the chance number was produced. This was the fact that immediately after hearing the chance number, I became aware of a dog barking in the distance and J's associations showed that he had also heard the dog. The question is this: Was there something in the aggregation of digits in the chance number which somehow conveyed to me J's prior awareness of the barking dog and directed my attention to this remote sound? On the other hand, had the barking, after all, been simultaneously and independently recognized by J and me? It is hard to believe that it was a haphazard phenomenon that just happened to emerge at the same time as the chance number, since it was precisely mentioned in the ensuing associations. Even if it was an "accident," why did I so specifically become aware of the barking immediately after the chance number emerged? Quite apart from this, how are we to regard the three-pronged "coincidence" revealed by examination of (a) J's chance number—reduced total, 8; (b) J's associations

leading to *ate*—homonym *eight* or 8; (c) addition of letters in the words given by J in his associations—reduced total, 8?

The junction between mathematics and language suggested in the *ate* = 8 equivalence above is worth noting, not only because of the link between the six-letter word *Schuld* and the figure 6 in the earlier example, but because a later example will show a still more intimate linking. In relation to this particular equivalence, Ella Freeman Sharpe reports in her book *Dream Analysis* (London, Hogarth Press, 1949), p. 92: "A dream of the number 180 was interpreted for me during an analytical session as meaning, 'I ate nothing.' "

Case O: In the course of this inquiry I decided to test whether it would be possible to work with two "chance numbers" at one time. I wrote down the figure groups 73,912 and 43,821. The sums are:

(a) $\Sigma 73{,}921 = 22;\ 2 + 2 = 4$

(b) $\Sigma 43{,}821 = 18;\ 1 + 8 = 9$

Instead of following the orthodox psychoanalytical method of associating to the original chance numbers, I associated the products; (a) led me to thoughts of my wife, Anna. It then suddenly occurred to me that the name Anna contains *four* letters; (b) led me more swiftly to thoughts of my wife through the associations *nine—nones—nonies—Noni*. My wife also has the Christian name Noni, by which she is often called.

I then added the products of (a) and (b).

(c) $4 + 9 = 13;\ 1 + 3 = 4$

This immediately suggested a joint reference to my wife, since both her Christian names have four letters, and since the separate products had pointd to those names.

On inspecting my "chance numbers," I noted that only two figures were missing, 5 and 6. The combined number, 56, promptly suggested the street number of my house. I added the two figures:

(d) $5 + 6 = 11;\ 1 + 1 = 2.$

This suggested first the two figures of my wife and myself, then, once again, the *two* Christian names which had occurred earlier. I found this repeated association to my wife a little baffling, since I conceived there must be some *special* reason for it. As a last resort I added the products of (c) and (d):

$4 + 2 = 6$

This number recalled to my memory a dream which my wife had related to me several days earlier. According to her pleasant (but perhaps not altogether philanthropic) dream, I had received from America a check for the sum of exactly £639/12/3 (slightly more than $2,000). I added these figures:

$6 + 3 + 9 / + 1 + 2 / + 3 = 24 : 2 + 4 = 6.$

I did not have to probe deeply into the recesses of my being to find that I would welcome such a substantial check, and, in fact, had been hoping for one precisely from America, as my wife well knew. Nor, since it was particularly her dream and concerned with the manipulation of figures, was it altogether astonishing that I should link her name or names with this (borrowed) wish-fulfillment. But, once again, there is the issue of how far

coincidence can be countenanced in these results.

Case P: A dream which I had a few weeks after examining these particular "chance numbers" is worth recalling, because, as will be evident in due course, the "motive" of the dream and the "motive" behind my selection of numbers have a good deal in common. In this dream of mine, the nonsense-word *trocheesive* appeared. On waking, I set to the task of attempting to unravel it. A *trochee* is, of course, a metrical foot, consisting of a long syllable followed by a short syllable. It seemed that the nonsense-word represented an inversion and should read *ive trochees* or, more clearly, *I've trochees.* If this was correct, it would suggest that some uneven stress was intended—possibly a limp. In this case, the solution should read *I've limps,* or *I've a limp,* or, more simply, *I limp.* This tentative solution was interesting because, in fact, I *do* limp. However, the examination seemed superficial, and corroboration was clearly needed.

Following a technique I have developed of rapidly writing words to secure associations, the nonsense-word *trocheesive* was then examined. Instead of tackling it directly, however, I broke it into three syllables—*tro, chee* and *sive.* My written associations were:

TRO: Pony, no, going, Roman, tell, see, *me, relation,* Kenny, drive, nobody, taking, *fourteen, six,* no one, let, *me, relation.*

CHEE: Nipple, breast, Anna, ma, Betty, Hatton Street, Karori, lines, hill, school, fountain, court, boy, fight, face, eye, tip, *grandfather.*

SIVE: Sieve, garden, *grandfather.*

To begin with, I was struck by the appearance of two numbers 14 and 6, in the first list of associations. Simple addition, along the lines followed in this paper, gave the result:

$\Sigma 14 = 5 + 6 = 11; 1 + 1 = 2$

It also seemed significant that the associations, *me, relation,* had appeared twice in the *tro*-group and that there had been associations in both the other groups to *grandfather.* It seemed possible that *me, relation* was a disguised reference to *grandfather,* so I prepared to give associations to this latter word. On writing it, the fact that it contained 11 letters became clear. By simple addition, i.e. $1 + 1$, this number gave the product 2, which was also the product of the earlier sum. It seemed not without point to begin by taking associations to this word *two.* These were:

TWO: Anna, us, street, here, bay, run, car, Hans, sick, stipple, nipple, Anna, ma, Betty, Hatton, Pope, rode, bicycle, Marjorie, ma, home, room, books, *grandfather.*

Once again, the 11-letter product *grandfather* had emerged. At this stage, it suddenly became obvious that the original nonsense-word *trocheesive* also had 11 letters. In short, an independent verification had appeared for the associations to *grandfather* which had been made earlier. The next step was to associate to *grandfather,* with the following result—

GRANDFATHER: Garden, hedge, Marjorie, trees, stone, roof, run, cart, bread, plums, walnuts, fowls, playing, shed, parties, side, street, gate, swing, farm, maid, room, lino, bed, window, uncle, hair, kitchen, fire extinguisher, Alfred, £5, Sydney, *Sidney Baker.*

Here, of course, the train of associations had arrived back at myself. A moment's reflection showed that there were 11 letters in the two words *Sidney* and *Baker.*

There seems little need to advertise my private obsessions for the benefit of readers by presenting my subsequent associations in detail. It is essential, however, to point out that these associations led to financial issues, and that the words *financially crippled* suddenly emerged. In turn, an immediate link with *I limp* became clear, together with the original nonsense-word *trocheesive*, which had produced an *I limp* association of a physical and not financial type in the first place.

The reason I have gone into this examination in some detail is that the two "chance numbers" studied earlier were also financially oriented. It will be recalled that one of the key sums was—

(d) $5 + 6 = 11; 1 + 1 = 2$

In short, the product 2, reduced by simple addition from 11, i.e. $1 + 1 = 2$, was highly significant to me.

Now, I do not hold out any great virtue for the method of reaching this conclusion, but it is quite clear that numbers, even if presenting no solution in themselves, can be important guides and might well be worth more attention than is commonly applied to them.

Sharpe's view in *Dream Analysis* (p. 91) that "dreams containing numbers are often difficult to analyze" will scarcely be disputed, but her added comments ". . . and they do not always repay the inquiry" may be open to some amendment.

SUMMARY

Starting from the psychoanalytic view of coincidence as applied to numbers, a series of instances taken from Freud, psychoanalytic literature, and the author's own experience is analyzed to show an apparent ability of the unconscious or preconscious mind to perform mathematical operations distinct from the conventional kind. These operations involve essentially the selection of series of numbers, the sum of whose digits is remarkably constant and somehow significant within the subject's frame of association.

RESUMEN

Partiendo de la concepción psicoanalítica de la coincidencia en su aplicación a los números, se analiza una serie de casos provenientes de Freud, la literatura psicoanalítica, y la experiencia personal del autor, para demostrar una habilidad aparente de la mente inconsciente o preconsciente de hacer cálculos matemáticos distintos a los corrientes. Estos cálculos tienen que ver esencialmente con la selección de series de números, la suma de los cuales es notablemente constante y de alguna manera significante dentro de los límites del poder asociativo del sujeto.

RESUME

Partant de la notion psycho-analytique de la coincidence appliquée aux nombres, une série de cas tirés de la bibliographic psycho-analytique de Freud et de l'expérience personnelle de l'auteur est analysée dans le but de démontrer l'aptitude apparente de l'esprit inconscient ou préconscient pour effectuer des opérations mathématiques distinctes du procédé habituel. Ces opérations comportent essentiellement le choix d'une série de nombres dont la somme des chiffres est remarquablement constante et présente une certaine importance dans le cadre d'association du sujet étudié.

ZUSAMMENFASSUNG

Ausgehend von der psychoanalytischen Anschauung des Zufalls in Bezug auf Zahlen, wird eine Serie von Begebenheiten, die den Schriften Freuds, der psychoanalytischen Literatur und den persöonlichen Erfahrungen des Autors entnommen sind, analysiert. Es ergibt sich die scheinbare Fähigkeit des Unbewussten oder Vorbewussten mathematische Operationen auszuführen, die sich von der gewöhnlichen Art unterscheiden. Der wesentliche Punkt besteht in der Wahl von "zufälligen" Zahlen, deren Einzelziffersummen überraschend konstant und dem Assoziationsgebiet der Subjekte verwandt sind.

DISCUSSION

Marvin Weinberg, M.D.

Dr. Baker's intriguing study raises the question whether certain insufficiently-examined performances of the nervous system, such as the *Id-arithmetic*, may reveal something of the operational character of the system as a mechanism, a problem that has earlier interested this writer.* A degree of caution is, of course, wanted in such interpretations in order not to invite preoccupation with performances that are genuinely gratuitous or with results that may have arisen elsewhere than in purposeful operations of the Unconscious — for example, in the ordinary properties of numbers. Any striking arithmetical result may have, as Dr. Baker points out, either "pure coincidence" or unconscious purpose as its origin. The properties of numbers are a third possibility, and we should be prepared to consider a fourth and a fifth.

Freud evidently allowed more room for honest coincidence than any of his disciples, just as he experienced more serious perplexities than have been duly transmitted over the years. It is nearly certain, at least, that Freud was not prepared to refute the known behavior of digits in a decimal system. Hence we ought to distinguish as carefully as possible among "pure coincidences," seeming coincidences which arise out of the numbers themselves, and useful hints of unconscious performance.

It may have been unfortunate, for the present purposes, that Haitzmann chose to make 9-year pacts with the devil. Not only did the number 9 have special significance for this patient, so that the sums of digits of such dates as September 24, 1668, and September 24, 1677, add up curiously to 9, but in addition one must find that the digits of *all* dates 9 years apart will add up to the same, number, whether it be 9 or any other. What they add up to is Haitzmann's concern, and is clinically suspicious; but that they are the same after 9 years is neither clinical nor coincidental, but a commonplace property of the decimal system of numbers. Again, the fact that May 9, 1678, adds up to 9 may have the unconscious significance Dr. Baker points to, while May 9, 1669, does not.

Adler's number 1734 led him, by some associations, to 6, and 6 also is the residue of 1734 after one has cast out nines. But in order to explain this choice of number we must understand the history of the times by a rather imperfect hindsight, and ascribe guilt (or more properly, fault), *Schuld*, to Freud and so enable Adler to improve upon his doctrines. Even a moderate critic might suggest that the interpretation is tenuous.

In the case of Freud's patient whose birthday was the 27th vs. the 26th of the month, Freud added 10 here and subtracted 10 there in a manner that Dr. Baker finds arbitrary. Of this we can hardly be sure. What does seem perfectly certain is that Freud closely related the patient's inventions to the difficulties of his life, essentially, if not literally. But it is equally certain that, of two numbers which differ by 1, the addition of 10 to the smaller and subtraction of 10 from the larger will always yield a new pair giving the same residues as the old pair. This is not the result of any astute performance by the patient's unconscious but is the usual effect of adding or subtracting 9 (or 10 — 1).

The patient born in 1882, who was 28 years old in 1898 (or 16 years later), affords an example

*Am. Scientist 39: 74, 1951.

of two numbers, 1882 and 28, with the same residue, 1. Yet the same example contains also 1898 (=8) and 16 (=7), to which no notice has been given.

It is quite true that a random number is impossible in subjective life. Mathematicians who must use random numbers obtain them from deliberately compiled *tables of random* numbers which are as impersonal as a table of logarithms; for it is realized that to "think of a number, any number at all" never gives an indifferent result. On the contrary, every choice one makes is significant and interested. *How* significant is another matter. Numbers, like every other subject matter, can be manipulated in such a way as to divulge what one partly wishes to conceal, and the process therefore has clinical interest; but only to the extent that the matter itself has interest. There was an epoch in clinical psychiatry when no detail was too insignificant, as in the better detective fiction, but one prefers to think that present techniques are more cogent, realistic, and time-saving.

One warning is essential in regard to the ways numbers can be manipulated. It is true that residues of numbers and of their sums remain the same even when the order is changed, zeros are added or removed, and the position of the decimal place moved about. These properties of numbers are often useful in verifying an arithmetical result, as by casting out nines. But it should be remembered that even when five or six digits appear in the argument, an agreement obtained in this way does not represent one chance in several thousand; it represents 1 chance in 9. The opportunity for apparent coincidence is very large, indeed enormously larger than might be thought from inspecting the numbers involved.

It therefore seems that "pure coincidence" is a negligibly small factor in the reappearance of certain digits, calculated out in the way Dr. Baker has done. As Dr. Baker contends, unconscious operations may account for some of the apparent coincidences. The ordinary properties of numbers probably account for the preponderance of them.

CLOSING DISCUSSION

Sidney J. Baker

Dr. Weinberg's cautionary note is well-justified; I am myself by no means certain how far the findings in my paper can be accepted for general application or even what precise constructions can be put on them. I make the latter point because an unresolved issue emerges from the cases given and its solution is necessary before satisfactory constructions can be made.

The issue is this: Do the cases given serve as evidence of mathematical processes in the Unconscious or are such processes localized in the Preconscious? Or, perhaps more important, are processes involved in both the Unconscious and the Preconscious and, if so, how do they operate?

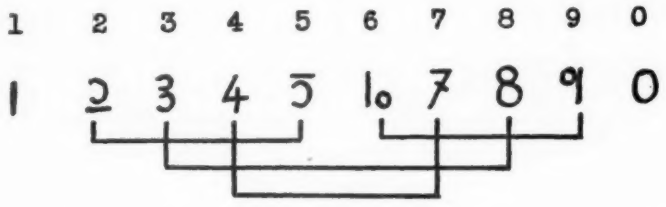
Some years ago, Ernest Jones wrote a paper on "The Problem of Paul Morphy: A Contribution to the Psycho-Analysis of Chess" (*International Journal of Psycho-Analysis*, 12:1-73, 1931). In this he remarked: ". . . One wonders whether the so-called intuitive chess sense does not imply a special power of preconscious calculation. The experiments Milne Bramwell carried out showed that the subconscious capacity for arithmetical calculation, as tested in hypnosis, far exceeds the conscious capacity, and the same may well hold good for the computation of chess moves." I have not been fortunate enough to see Bramwell's findings, but Jones's comment on "a special power of preconscious calculation" has provoked a number of reflections which may be relative to the problems raised in my paper.

Four examples given (Cases D, E, N, and P) point to some direct and important link that occurs occasionally between "chance numbers" and words. This link would occur in the Preconscious, where impulses and images emanating from the Unconscious, after being censored by the Superego, come into conjunction with word-residues and so find a channel into the conscious via preconscious mnemic systems. The starting point, clearly enough, would be the Unconscious. Since all images in the Unconscious are framed in sexual terms, we are led to inquire into the way in which digits could be interpreted in such terms. Since there are only nine digits from 1 to 9 to examine—or ten if it is preferred to take the full range 1234567890 which represents our complete battery of figures—the task should not be beyond human endeavor. To begin with, the figure 1 is psychoanalytically recognized as a phallic

symbol, and 0 as a kteis or female genital symbol; 3 is commonly accepted as a symbolic reference to the male genitalia or to the aggregation of the three female orifices, urethra, vagina and anus. At this stage, however, agreement seems to cease. From the wide reading I have made into psychoanalytical interpretation of the other digits, the matter seems to depend on the inspiration of the moment.

With this in mind, I draw attention to a brief paper by Wyman Guin on "Numerals and the Sexuality of Scientific Investigation" (*The Psychoanalytic Quarterly*, 23:490-496, 1949) in which he suggests that digits produce "a formal design." He sets this design out as follows:

FIGURE 1

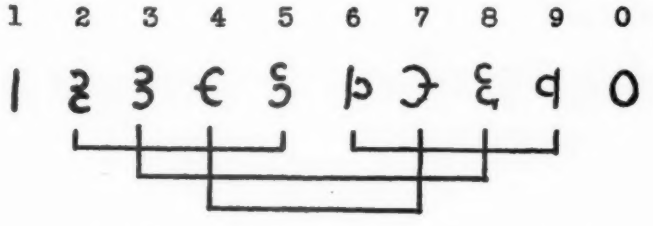


Guin describes the figures 1 and 0 as "polar" and suggests that links are established between the other figures as follows: 2 is "rotated once in two dimensions" to derive 5; 6 is similarly rotated to derive 9; 3 is "half of 8"; and 7 with a line across its stem, as is common in Europe, is "a mirror image of 4 or it may be rotated once in three dimensions to obtain 4."

I may be mistaken, but some aspects of this argument seem to place considerable strain on our credulity. It lacks the consistency and reliability which are among the outstanding features of unconscious activity—they are neither logical (from the viewpoint of the Ego) nor paleological (from the viewpoint of the id).

Insofar as we can suspect that the Unconscious has any truck with figures, those figures should be reducible to the sexual symbols with which the unconscious is preoccupied. Those symbols are the straight line, the cleft and the circle.

FIGURE 2.



Depending on what level of libidinal differentiation is tapped, the straight line can symbolize the nipple (oral level), stream of urine or urinary penis (urethral), fecal mass (anal), and the clitoris or erect—and hence sexual as distinct from urinary—penis (phallic). The cleft symbolizes the minute nipple apertures and the oral cavity and, hence, the mouth-filling breast (oral), the male or female urethral apertures (urethral), the external aperture of the cloaca (anal), the vagina, and the penile aperture (phallic). The circle has symbolic significances similar to those of the cleft.

With these points before us, I suggest it is possible to modify Guin's numerical schema as follows:

In the above, the formal outlines of our modern numerals have lost their sharpness, but anyone who takes the trouble to write them rapidly will see that the resemblances return. Equally important, we see that in each case where Guin suggests a link between certain figures, this involves no more than a simple reverse of the symbol concerned. Moreover, this has been accomplished solely by the use of basic symbols. To this extent—whatever else has been sacrificed—some measure of consistency has been obtained.

Now, where would these rudimentary symbols be found in the human mnemic systems? My view is that they would be found in the lower levels of the Preconscious. When impulses or images generated on certain of the differentiated levels of the Id seek an outlet, they must first pass through the Superego. This converts the original nakedly-sexual impulse or image into a form acceptable to the Ego. Hereby, the image is converted into the rudimentary forms of line, cleft, or circle, and depending upon the strength given to one or other of these, merges into one of the formal numerical symbols in Figure 2. This symbol is borne outward through the Preconscious where it meets and merges with the appropriate word-residues, and is ultimately revealed in a recognizable Ego form.

This leads me to suggest that the title of my paper "The Mathematics of the Unconscious" is probably misleading; while originating in the Unconscious, it is in the Preconscious that these mathematical processes become recognizable.

This, of course, does not answer the question that inevitably arises as to how the psychic mechanism exploits what appears to be a process of simple addition. I personally suspect that it may be associated with the underlying principle of psychic economy upon which the Unconscious works and which tends to disintegrate as it nears the surface of consciousness.

It may, perhaps, be suggested that the mechanics of the process is somewhat as follows: An impulse or image is roused from one of the differentiated levels of the Id and, after censorship by the Superego, comes into conjunction with the appropriate primary image or constellation of images in the lower levels of the Preconscious. Since this image or image-group is made up of any combination of the three basic symbolic forms—line, cleft and circle—the path is open to exploit any of the rudimentary numerals in Figure 2 by routine preconscious processes of elaboration and conversion. These processes always operate in terms of addition. In this way, the original basic image becomes, so to speak, "ornamented" and disguised by the addition of related rudimentary numerical forms. But the original basic image, being charged with the greatest quantity of affect from the Id, retains its relative strength over the attendant images. It emerges in strong disguise in the Conscious and only when we dismantle it by a process of "reduced addition" can we see what basic image was roused in the Preconscious in response to stimulation from the Id.

It should be added that I am by no means fully satisfied with the numerical image-residues offered in Figure 2; they are too well developed. I hope, however, that someone may be stimulated by the thoughts in my main paper and this attendant note to focus some attention on the matter. I suspect that nothing will give us a better insight into the mechanics of human thought than elucidation of this problem.

A Study of the Personality Structure of the Prisoner in Hawaii

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This paper presents the findings of a study made during 1948-49 in which newly admitted prisoners to the Oahu (Territorial) Prison were examined by means of the Rorschach, Wechsler-Bellevue, and Bender Gestalt tests. On the basis of this testing and an evaluation of the data from the social history, as well as a brief interview with the prisoner, an overall psychological profile was prepared.

The first table shows the comparative incidence of crime in the population under study for different racial groups. There were singularly few Chinese; Hawaiian, Puerto Rican, Filipino, and Portuguese groups contributed somewhat above expectancy for their respective population incidence.

Table 1
Differences in Incidence of Crime in Hawaii for Varied Racial Groups
(1948—1949)

	Criminals Admitted to Oahu Prison %	Confidence Interval %	Incidence in Population (1948) %
Hawaiian	8.9	4—16	2.0
Chinese	0.6	0—5	5.6
Caucasian	8.3	4—15	16.0*
Japanese	6.4	2—12	32.6
Puerto Rican	9.6	5—18	1.8
Filipino	11.5	5—19	9.9
Portuguese	9.6	5—18	7.4*
Korean	0.6	0—5	1.4
Others (mixed)			

*Data based on population incidence in 1938-39.

Table 2 presents data on the mean chronological ages according to racial group, nature of crime, and type of overall psychological profile. Highly significant differences were obtained between mean ages of those who committed crimes against property and sex crimes, and between mean ages of those with moderately neurotic profiles and those with psychological profiles suggesting mixed pathology. A significant difference was obtained between the mean age for all prisoners and part-Hawaiians.

Table 3 presents data on the relation of the level of the socio-economic status and the quality of parental guidance to the type of crime and nature of the overall psychological profile. The assessments suggested here are very crude indeed but nevertheless these findings confirm the generally accepted view that low socio-economic status is significantly related to inadequate parental guidance and type of crime committed. It should be noted that

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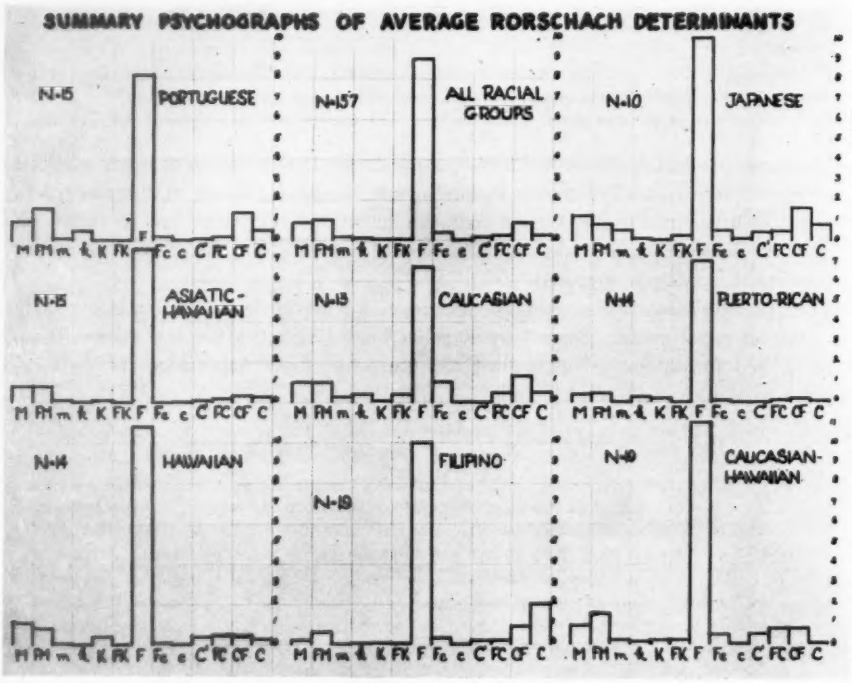

FIGURE 1. Average Rorschach Profile for Varied Racial Groups.

—even if we admit to large error in these assessments—there can be no denying that the vast majority of the population under study are products of inferior and very inferior home backgrounds.

Twenty-six per cent of all crimes were committed by those 20 years of age and younger; 56 per cent by those 24 years of age and younger; 73 per cent by those 28 years of age and younger. Of those who committed crimes against property, 80 per cent were 28 years of age and younger.

Seventy-three per cent of crime was against property; 10 per cent against person; and 17 per cent were sex crimes.

The mean I.Q. for the entire group was 87.45 and the standard deviation 15.56.

An overall psychological profile suggesting a mild neurotic pattern of behavior was found in 22 per cent of the group; 38 per cent were regarded as moderately neurotic; 9 per cent showed evidence of severe neurotic struggle; 26 per cent showed mixed pathology; 5 per cent showed psychological profiles suggestive of convulsive disorder, organic brain damage, and outright psychosis.

Figures 1, 2 and 3 present graphically the average Rorschach profiles for varied racial groups, overall psychological profiles, and types of crime.

The relative significance of the observed variation for the more critical determinants is expressed first in terms of χ^2 and, more efficiently, by means of variance analysis. These appear in Tables 4, 5, and 6.

It will be noted that the total variance in the selected determinants (Table 6) has been partitioned in one instance between sources of variance due to differences in racial group and differences in psychological profile. Variation in CF between racial groups and in FM between psychological profiles were observed to be significant; and highly significant values were obtained for variation in M and FC between psychological profiles.

Table 2
Mean Chronological Ages

Race		
Hawaiian	(14)	26.36 years
Part Hawaiian	(38)	23.12 years
Japanese	(10)	24.20 years
Caucasian	(13)	32.46 years
Puerto Rican	(14)	26.79 years
Filipino	(19)	28.82 years
Portuguese	(15)	28.63 years
Mixed Racial Groups	(34)	26.03 years
Nature of Crime		
Crime Against Property	(115)	24.55 years
Crime Against Person	(15)	32.90 years
Sex Crime	(27)	30.21 years
Nature of Overall Psychological Profile		
Neurotic (mild)	(35)	24.79 years
Neurotic (moderate)	(60)	24.43 years
Neurotic (severe)	(14)	25.07 years
Mixed Pathology	(41)	30.99 years
All Prisoners	(157)	26.27 years

When the total variance was partitioned between racial groups and types of crime, significant values were obtained for the FM determinant, both between racial groups and between types of crime; and in FC between types of crime, and a highly significant value was obtained in variation in CF between racial groups.

Finally, when the total variance was partitioned between sources of variation due to psychological profiles and varied types of crime, significant values were observed in variation in M, FM, and FC between psychological profiles.

Figure 4 shows the Bender Gestalt reproductions for the group with psychological profiles suggesting mixed pathology.

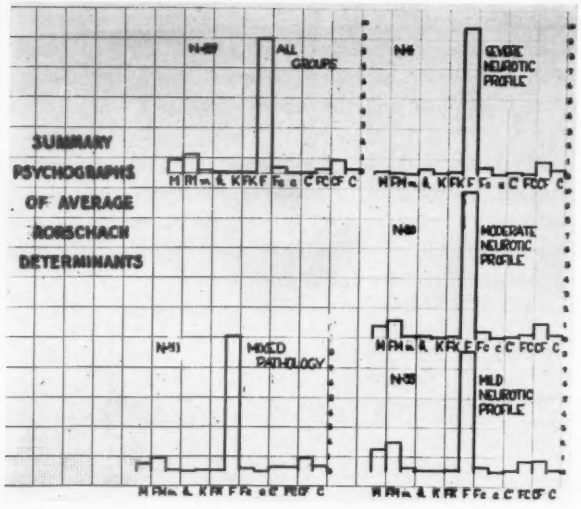

FIGURE 2
Average Rorschach Profile for Overall Psychological Profiles.

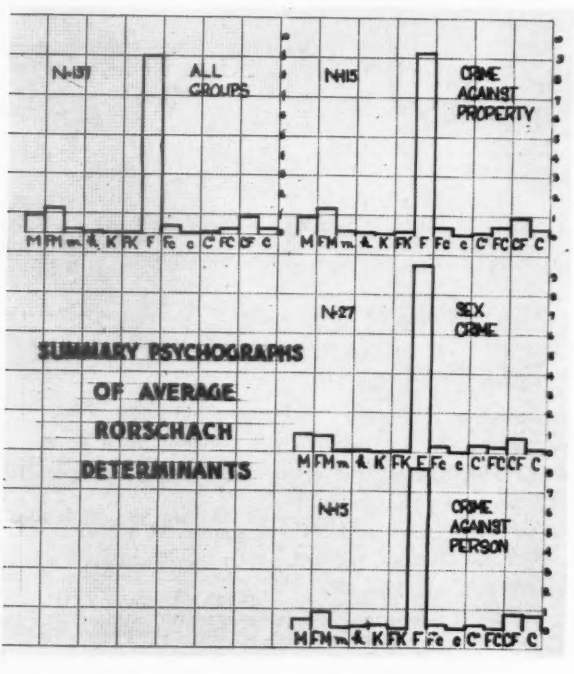

FIGURE 3
Average Rorschach Profile for Types of Crime.

Table 3

Relation of Level of Socio-Economic Status to the Personality Structure of the Prisoner
(Hawaii, 1948-49)

Personality Structure of the Prisoner	Level of Socio-Economic Status: Very Inferior	Inferior	Average or Better	Total	d.f.	Chi-Square
Neurotic (Mild)	8	19	8	35	4	6.7476
Neurotic (Moderate-Severe)	21	36	17	74		
Mixed Pathology	15	30	3	48		
	44	85	28	157		

Relation of Level of Socio-Economic Status to the Quality of Parental Guidance During the Formative Years

Socio-Economic Status	Quality of Parental Guidance: Very Inferior	Inferior	Average or Better	Total	d.f.	Chi-Square
Average and Better	0	11	17	28	4	137.6845**
Inferior	18	63	2	83		
Very Inferior	39	5	0	44		r = 0.79*
	57	79	19	155		(d.f. 7)

Relation of the Quality of Parental Guidance During Formative Years to the Personality Structure of the Prisoner

Personality Structure of the Prisoner	Quality of Parental Guidance: Very Inferior	Inferior	Average or Better	Total	d.f.	Chi-Square
Neurotic (Mild)	13	18	4	35	4	4.1022
Neurotic (Moderate-Severe)	28	34	12	74		
Mixed Pathology	17	26	2	45		
	58	78	18	154		

Relation of Level of Socio-Economic Status to the Types of Crime Committed

Types of Crime	Level of Socio-Economic Status: Very Inferior	Inferior	Average or Better	Total	d.f.	Chi-Square
Crime Against Property	39	60	17	116	4	10.8287*
Crime Against Person	3	6	5	14		
Sex Crime	2	19	6	27		
	44	85	28	157		

(Significant values are indicated with a single asterisk; highly significant values with two asterisks)

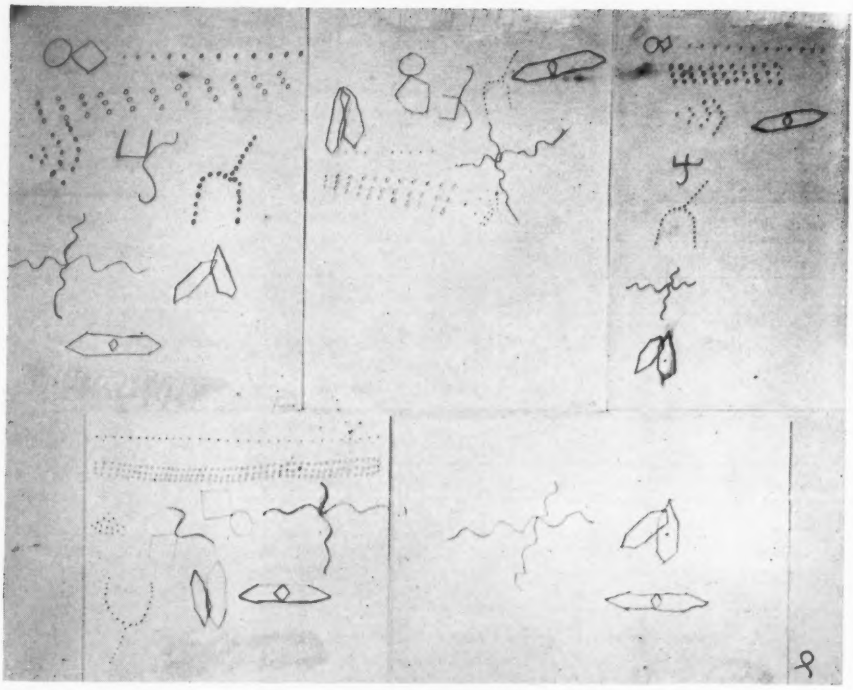

FIGURE 4. Bender Gestalt Reproductions for the Group with Psychological Profiles Suggesting Mixed Pathology.

Table 4
Chi-Square Values for Rorschach Determinants in Different Racial Groups and Varied Psychological Profiles and Types of Crime

	Racial Groups		Psychological Profiles		Types of Crime	
	d.f.	Chi-Square	d.f.	Chi-Square	d.f.	Chi-Square
M	12	18.3123	6	22.8361**	6	2.8114
FM	18	16.7516	6	23.6565**	6	8.9972
FC	12	15.8218	4	12.7452*	4	5.1039
CF	18	23.2780	6	15.0200*	6	5.2046
C	6	29.09**	4	2.1229	4	8.1950

(Significant values are indicated with a single asterisk; highly significant values with two asterisks.)

Table 5

The Relative Significance of Chi-Square for Rorschach Determinants in Varied Comparisons

	d.f.	Chi-Square
Relation of Type of Crime to Overall Psychological Profile	4	11.8762*
Distribution of the M Determinant in All Cases and in Cases of Psychological Profiles Suggesting Mixed Pathology	3	4.1775
Distribution of the M Determinant in Psychological Profiles Suggesting Mild Neurotic and Mixed Pathology	3	13.0573**
Distribution of the M Determinant in Psychological Profiles Suggesting Mild and Moderately Severe Neurotic Profiles	3	15.5478**
Distribution of the FM Determinant in Mild and Moderate-Severe Profiles	3	22.0679**
Distribution of FM Determinant in Mild Neurotic and Mixed Pathology Profiles	2	16.7244**
Distribution of the FM Determinant in Filipino and Japanese Groups	2	1.5568
Distribution of FM Determinant in Hawaiian and Caucasian (Not Including Portuguese) Racial Groups	2	1.3237
Comparison of the CF Determinant for all Prisoners and Those Who Committed Sex Crime	3	1.8628
Comparison of Filipino and All Other Racial Groups With Respect to Type of Crime	2	14.81**
Relation of Racial Group to Type of Crime	12	21.9626*

(Significant values are indicated with a single asterisk; highly significant values with two asterisks.)

Table 6

Mean Square Values for Determinants in the Rorschach

I. *For Different Racial Groups and Varied Psychological Profiles*

Rorschach Determinant	Between racial groups (6 degrees of freedom)	F	Between psychological profiles (2 degrees of freedom)	F
M	1.94	2.00	8.52	8.78**
FM	2.57	1.02	14.84	5.87*
FC	0.39	1.70	2.30	10.00**
CF	3.44	4.35*	0.69	0.87
C	0.87	1.18	0.39	0.53

II. *For Different Racial Groups and Varied Types of Crime*

Rorschach Determinant	Between racial groups (6 degrees of freedom)	F	Between types of crime (2 degrees of freedom)	F
M	2.10	2.39	0.60	0.68
FM	2.93	3.91*	4.16	5.55*
FC	0.63	2.74	1.12	4.87*
CF	3.61	11.64**	0.36	1.16
C	0.91	1.52	0.98	1.63

III. *For Different Psychological Profiles and Varied Types of Crime*

Rorschach Determinant	Between psychological profiles (2 degrees of freedom)	F	Between types of crime (2 degrees of freedom)	F
M	10.47	7.59*	1.21	0.88
FM	14.34	10.10*	3.48	2.45
FC	2.45	11.14*	1.14	5.18
CF	0.81	0.27	1.67	0.55
C	0.47	1.96	0.92	3.83

(Significant values are indicated with a single asterisk; highly significant values with two asterisks.)

SUMMARY

1. The data reveal the presence of rather striking and unmistakable psychopathy in a group of prisoners admitted during 1948-49 to the Oahu Prison in Hawaii.

2. The observed psychopathy is described in terms of known neurotic and psychotic mechanisms suggesting little need for the use of the diagnostic label of psychopathic personality.

3. It is felt that the Bender Gestalt test contributes measurably to the overall psychological profile and should be used routinely in conjunction with the Rorschach and other projective techniques.

4. Although the data suggest that emotional dysfunction is a singular feature of the personality structure and that adverse socio-economic and cultural influences are significantly related to crime, we are still in the dark about the nature-nurture relationships involved.

RESUMEN

1. Los datos revelan la presencia de una psicopatía notable e inequívoca en un grupo de prisioneros admitidos durante el período 1948-49 al presidio de Oahu, Hawaii.

2. La psicopatía observada se describe en referencia a mecanismos neuróticos y psicóticos conocidos que indican la poca necesidad de aplicarle la etiqueta diagnóstica de personalidad psicopática.

3. Se considera que el examen Bender Gestalt contribuye mesuradamente al cuadro psicológico general, y debe usarse rutinariamente en conjunto con el examen de Rorschach y otras técnicas proyectivas.

4. Aunque los datos sugieren que trastornos emocionales son una característica de la estructura de la personalidad, y que influencias socio-económicas y culturales adversas están significantemente relacionadas con el crimen, todavía desconocemos la naturaleza de las conecciones aplicables entre los ambientes natural y social.

RESUME

1. Les observations relevées révèlent la présence d'une psychopathie indéniable et assez marquée chez un groupe de prisonniers admis au cours de 1948-49 dans la Prison d'Oahu aux Iles Hawaii.

2. La psychopathie observée est décrite en termes de mécanismes neurotiques et psychotiques connus, de sorte qu'll n'y a guère besoin d'appliquer la désignation diagnostique de personnalité psychopathique.

3. Il est estimé que le test Bender Gestalt contribue à un degré appréciable au profil psychologique d'ensemble et qu'il convient de l'employer à titre régulier en relation avec la technique Rorschach et les autres techniques d'extériorisation.

4. Bien que les observations faites suggèrent que la disfonction émotive est une caractéristique particulière de la structure de la personnalité et que les influences socio-économiques et culturelles contraires ont une relation significative avec le crime, nous sommes encore dans l'ignorance quant aux rapports nature-éducation en jeu.

ZUSAMMENFASSUNG

1. Die Angaben zeigen die Anwesenheit einer recht eindrucksvollen und unmissverständlichen Psychopathie als Kennzeichen einer Gruppe von Häftlingen, die in den Jahren 1948-1949 in das Oahu Gefängnis in Hawaii eingliefert wurde.

2. Die festgestellte Psychopathie wird im Rahmen bekannter neurotischer und psychotischer Mechanismen beschrieben, und es erscheint deshalb wenig Anlass, sich der diagnostischen Bezeichnung von "psychopathischer Persönlichkeit" zu bedienen.

3. Es besteht der Eindruck, dass der Bender-Gestalt-Test einen beträchtlichen Beitrag zu dem gesamten psychologischen Profil liefert und gewohnheitsmässig in Verbindung mit dem Rorscharch-Test und anderen projizierenden Methoden anzuwenden ist.

4. Obwohl die Angaben nahelegen, dass Gefühlsstörungen ein einheitliches Kennzeichen der Persönlichkeitsstruktur sind und dass ungünstige sozio-ökonomische und kulturelle Einflüsse einen bedeutsamen Zusammenhang mit der Kriminalität haben, tappen wir immer noch im Dunklen, was den Zusammenhang zwischen natürlichen Anlagen und Umgebungseinflüssen betrifft.

Creativity in a Middle-Aged Psychotic

A CLINICAL CASE REPORT AND DISCUSSION

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Since it is unusual for chronic mental-hospital patients who have never engaged in esthetic activities to begin to do so after their illness and especially rare for such activities to take the form of relatively coherent literary production, the case of Mrs. C. is of interest.

Mrs. C. has been a patient for 13 years, psychiatrically assessed as a paranoid schizophrenic whose illness has been greatly modified by constitutional factors of a manic-depressive sort. She is 51, married, has two children, but has been divorced by her husband since her admission to the hospital. Mrs. C. is a rather poorly educated former copy-typist whose tests now indicate a low average intellectual level.

Before her illness and during her first decade as a patient she afforded no evidence of esthetic creativity. In the past three years, however, as a member of an art-group of chronic patients she has produced over 250 pictures which, in addition to the classic features of psychotic painting, display exceptional variety in content and treatment, an astounding flow of different images, notions and ways of approach. She has also spontaneously written a succession of novels which, despite their crudity, digressions, inconsistencies, and wild improbabilities, have a strange vividness and a distinctive character. In these she shows narrative power, good control and management of the sequence of events, skill in dialogue, a comparatively rich vocabulary, fertility of imagery, and a general capacity for sustained effort.

One of her more remarkable novels is entitled "Jack and the Beanstalk." Its hero, named The Car-Owner-Driver, is a wealthy bachelor of luxurious but effeminate tastes. In the first chapter he murders a friend named The Guest. After concealing the body he goes on a tour of the world including Rome, Egypt, New Zealand, and New York. He has extraordinary adventures with a professional dancing partner called My Lady Hireling, a medical man called Spesh or The Specialist and a bank-manager named Chappie. At each place where he stays The Car-Owner-Driver produces vast numbers of paintings and other works of art which he sells for great sums of money. Finally he returns to England, retrieves the murdered body and amid fantastic but powerfully described circumstances turns it also into works of art. The novel covers over 300 manuscript pages.

Another remarkable novel is entitled "Bill and Liz." The hero is the proprietor of an enormous baby-farm in Korea which has three departments: a maternity ward, an adoption center and a butchery business with a cookhouse annexed. The babies proceed from one department to the next, finally to be cooked for sale as pork and veal. The details of butchery and culinary preparation are described at length with the utmost *sang froid*. After various events the baby-farm is nationalized and taken over by the House of Lords. The hero is inveigled to England where he is for some time feted as a public benefactor but afterward taken to jail and electrocuted.

Mrs. C. has written several similar novels whose heroes have titles such as Count Paraldehyde. Both in her paintings and novels certain special contents recur many times, notably artistic productivity, sadistic murders, celibacy or virginity, prostitution, divorce, espionage, tours round the world, Parisian dancers, bathrooms, and perfume.

The immediate releasing factor in the patient's pictorial creativity could have been attendance at the sessions of the art-group. This attendance, together with the emphasis and value given to esthetic activities in the hospital, might have given the immediate impetus to literary creativity. Many chronic patients, however, have shared these influences, yet few have responded by producing such a variety of paintings, none by writing novels. An attempt was made, by psychometric testing, careful biograph-

ical investigation, and prolonged discussion with the patient about her works, to find out what additional factors were operative.

Six additional factors might be considered contributory to the release of creativity in the particular hospital situation: (1) a personality for whom esthetic productivity was something laudable and desirable; (2) the possession of latent talents in the effective use of words, pictorial representation and design, and the rapid formation of images; (3) a great complex of frustrations and conflicts from prepsychotic life which, although modified by the confusions and disturbances of the illness, were nonetheless ready to be worked over and temporarily resolved in creative activity; (4) a strong self-concept, warped yet not destroyed or enfeebled by the illness, and a need for achievement still fully operative; (5) a capacity for self-criticism diminished to an extent facilitating esthetic production without making it entirely chaotic; and (6) considerable energy and capacity for sustained effort.

The vividness and curious power of the novels derive from an interaction between Mrs. C.'s literary ability and her disturbed thinking. Without the former they would be merely confused, and without the latter quite dull. The maintenance of an effective self-concept and a high degree of energy seem to be associated with the manic-depressive component of the illness. Without this counteragent to the schizophrenic component, pictorial activity would probably have been less varied and literary activity nonexistent. The essential rôle of psychotic illness in arousing literary creativity in Mrs. C., however, seems to have been in diminishing her self-criticism. It appears certain that if her capacity for critically appraising herself and her products had not been blunted and coarsened, she would not have embarked on the enterprise of her novels. In this regard it may be said that mental disease may directly stimulate a form of esthetic creativity.

The Schizophrenias of Childhood

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I. INTRODUCTION

The schizophrenias of childhood afford a number of advantages to the researcher. They permit study of the schizophrenic process in relatively "purer culture" because:

a. Hereditary influences in children are more readily accessible to examination and evaluation than in adults.

b. Congenital contributions are also more readily investigated. The child is less remote in time from maternal physiologic forces that may have been operative *in utero*, and the effects of such forces have been modified to a smaller degree by subsequent individual neuroendocrinologic developments than in adults.

c. Somatic vicissitudes, internal psychological conflicts and environmental influences have been fewer and usually less complicated, further aiding investigative appraisal. Familial and social forces are also more available for study.

As a result, the schizophrenic process in children may be delineated in simpler and sharper perspective, particularly with respect to its etiologic and pathogenetic forces.

Contents of the Present Report

The present report presents in preliminary form:

a. A clinical evaluation of the effects of histamine on the schizophrenias of childhood based on intensive investigation of 8 patients and their parents.

b. A number of new findings bearing on the etiology, pathogenesis, and treatment of the schizophrenias in general, based on a broad background of investigation of nonconvulsive biochemotherapeutic agents in psychiatric disorders—histamine, thyroid, insulin and sex steroids.

Appreciation is expressed to *The Psychiatric Quarterly* and Dr. Duncan Whitehead, Acting Editor, for their co-operation in releasing this paper so that it could be published in this van Ophuijsen Memorial Volume. This report is a tribute to the humanity, vision and clinical acumen which led J. H. W. van Ophuijsen to devote particular attention and sympathy to the youngest victims of psychiatric disorders. Though Dr. van Ophuijsen did not live to see its completion, it was made possible only through his inspiration and encouragement. It was he who planned that as much as half of the case load of The Creedmoor Institute for Psychobiologic Studies should be comprised of children and adolescents. The first few patients were being worked up when his untimely death deprived him of what would have been a particular source of gratification to him—some new insights into the problem of childhood schizophrenia.

This communication is a composite of two papers presented at the Down-State (Psychiatric Institute, New York City) and Up-State (Syracuse) Inter-Hospital Conferences of the Department of Mental Hygiene of the State of New York in April, 1951.

c. The relationship of the above to some of the available data bearing on the genetic influences based on a brief analysis of genetic influences on schizophrenia which have been noted since the classification of the disease entity.

II. CLINICAL MATERIAL

The patients covered in the present report were the first eight childhood schizophrenics to be admitted to the Creedmoor Institute for Psychobiologic Studies during the year 1950. In each case, the diagnosis of schizophrenia was made independently by the reporting group. In several cases this diagnosis was found to be supported by earlier diagnostic findings, and in no case was it found to be at variance with competent earlier evaluation. (Table 1)

Table 1:
Summary of Clinical Data

NUMBER	AGE ON ADMISSION	SEX	AGE AT ONSET	TYPE ONSET	PREVIOUS THERAPY	RESULT	TOTAL DURATION (RECOGNIZED)	WEIGHT IN KGM.	HISTAMINE TOLERANCE (MIN/KGM.)	TOLERANCE MGM./KGM.	THYROID GM.	THYROID MGM./KGM.	AVERAGE SCORED IMPROVEMENT (15-22)	D.R.C. RATIO	CLOT BEHAVIOR (Syringe Test)	CLOT BEHAVIOR OF MOTHER	THYROID OF MOTHER
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1	9-3	M	2-0		20 ECT	U	7-9	29.6	0.1	.0033	5	.0101	4+	2.3	Opens	Opens Diffi.	Not Palpable
48	9-0	F	2-0		-	-	7-0	28.6	0.2	.0069	-	-	3+	2.7	Opens	Opens Easily	Not Palpable 32.4% I_2* Uptake, Normal Urine Curve
19	9-0	M	0-9	SUDDEN	ECT	TI	8-3	26.3	0.3	.0114	3.5	.0079	3+	3.7	Opens Diffi.	Opens	Palpable 33.9% I_2 Uptake, Sluggish Urine Curve
74	10-4	M	2-0		20 ECT	TI	8-4	47.7	1.0	.0209	5	.0062	3+	3.2	Opens	Opens Easily	Enlarged, Palpable 52.5% I_2 Uptake, Hyper Urine Curve
59	7-4	F	3-0		20 ECT	TI	4-4	31.3	0.6	.0188	-	-	2+	1.0	Opens Easily	Opens Diffi.	Thyroidectomy
73	5-4	M	3-0	INSIDIOUS	-	-	2-4	23.2	0.35	.0150	4	.0103	1/2 to 2+	1.1	Opens Easily	Opens Easily	Not Palpable. Medical History of Thyroid Disturbance in Adolescence. 36.4% I_2 Uptake, Sluggish Urine Curve
16	7-10	F	4-6		ECT	TI	3-4	19.1	0.36	.0163	4	.0126	1+	2.3	-	-	Enlarged, Palpable
43	7-2	M	4-0		-	-	3-2	24.9	1.3	.0524	3	.0072	0 to 1+	-	Opens Easily	Opens	Enlarged, Palpable 45% I_2 Uptake, Normal Urine Curve

U = Unimproved TI = Temporary Improvement * Radioactive Iodine

At least half of the patients gave the impression of physical immaturity for their age group. One evidenced sexual precocity, having pubic hair at the age of 7. The children's expressions were usually variable, generally inappropriate and frequently absorbed. Silliness and lability of mood with ready excitability were often noted. The patients were easily distracted and markedly inattentive. Gait was characterized by peculiarities in the majority of cases. Anxiety was not found to be as prominent in this series as reported by Bender.[1] In some patients, however, anxiety became more apparent with clinical improvement.

The more striking psychiatric characteristics of the group were in keeping with the reports of most other workers. They included:

1. Withdrawal from and reduction or lack of interest in the environment. (Seven of the patients showed marked withdrawal.)
2. Hyperactivity.

3. Bizarre behavior.
4. Speech disturbances, including echolalia, verbigeration and mutism.
5. Dereistic thinking.
6. Symptoms of regression.

Of the eight patients covered in the present report, seven were being continued on ambulatory therapy at the time of writing, while the eighth patient (No. 16) had been hospitalized by the parents for reasons of family convenience rather than clinical necessity.

Five of the patients were male, three female. Their ages on admission ranged from 5 years, 4 months, to 10 years, 4 months. History revealed that the character of onset in all was insidious, the closest recognizable age of onset being:

No. of Patients	*Age of Onset*
1	9 mos. (approx.)
3	2nd year
2	3rd year
2	4th year

Five of the eight patients had previously been treated with electroconvulsive therapy (ECT), with temporary improvement reported in four (Nos. 16, 19, 58, and 74) and no improvement reported in one (No. 1). Unfortunately, clinical details as to the kind and degree of improvement were not available. The parents usually described such response to ECT as reportedly occurred in terms of reduction of anxiety, distractibility and hyperactivity.

As for the size of the present clinical sample, it compares with the 60 cases which Lutz[2] noted in his review of the literature in 1937. Only half of these patients were less than 10 years old and Lutz held that of these only 14 indubitably had schizophrenia to which he added six cases of his own. It is also to be compared to the four cases on the basis of which Potter[3] set his diagnostic criteria and the 100 cases collected over a period of ten years by Lauretta Bender.[1]

III. PROCEDURE

After anamnesis, the patients were studied psychiatrically, psychologically, and physiologically. The psychological test battery included the Rorschach, Thematic Apperception, and Stanford-Binet tests, Figure Drawings and Lowenfeld's Mosaic. Laboratory procedures included complete blood count, direct eosinophil count, sedimentation rate and hematocrit determination—all approximately weekly; and in seven patients, blood cholesterol and epinephrine tolerance tests. Parents and siblings were called in both for psychiatric and psychologic evaluation and physiologic study. The detailed reports on these findings will be published elsewhere.

A course of therapy over a period of approximately three months was chosen for purposes of uniformity in this report, though some of the patients were continued on therapy beyond that point. Histamine acid phosphate was administered subcutaneously daily, five days a-week, beginning with a dose of 0.1 mg. of histamine base. This dosage was increased

with each succeeding day of treatment by, 0,5 mg. of histamine base until a diastolic blood pressure of zero was achieved, at which level the dosage was maintained. The dosage of histamine base that produced a diastolic blood pressure of zero in a given patient was taken as an index of the patient's tolerance to histamine. The technique of histamine biochemotherapy has been reported in detail elsewhere.[4]

IV. CRITERIA AND RESULTS

a. *Clinical Course:*

To permit better comparison and classification of clinical data, improvement was rated independently by the psychiatrist, the nurse, the psychologist, and the parents, on the basis of the following scale of grades:

++++	=	Marked improvement
+++	=	Moderate improvement
++	=	Slight improvement
+	=	Traces of improvement

The grades obtained (with the exception of the parents' report) were averaged and are herein referred to as "average scored improvement." This "average scored improvement" showed the following picture after a three-month course of therapy:

Grade	*No. of Patients*
4+	1
3+	2
2+	3
1+	1
0	1

The three patients who scored 3+ and 4+ were in the 9-year age group—with a total recognized duration of the symptomatology ranging from 7 years to 8.25 years, and a mean of 7.75 years. The onset of symptoms in all three of these patients occurred before the age of 2. The remaining five patients had a total recognized duration ranging from 2.3 years to 8.3 years and a mean of 4.3 years; in four of these patients, symptoms were recognized between the ages of 3 and 4.5 years. None of the patients showed any aggravation of symptoms during the course of therapy. (Table 2)

It appears from these results that the schizophrenic process in children, as in adults[5-14] may be favorably influenced by histamine biochemotherapy. No effort is made to relate the present results to those reported in the literature on ECT for want of common criteria and detailed protocols. It must be stressed that these patients were treated on an out-patient basis and that all the patients, except for one, are still being followed at the clinic.

One of the striking differences between the results in this series and those obtained in cases of schizophrenia in adults was that the highest degree of improvement was obtained in cases with the longest duration, while in the schizophrenias of adult life best results were obtained in cases of shorter duration. Since most of the children showing improvement were approaching the pubertal period, the possibility must be considered that endogenous endocrine changes in these patients may have contributed to the beneficial effects.

Table 2

SCORING OF CLINICAL AND PSYCHOLOGIC TEST CHANGES							TEST CHANGES									BEHAVIOR	
NUMBER	AVERAGE SCORED IMPROVEMENT (13–22)	PSYCHIATRIST GRADING OF IMPROVEMENT	NURSE GRADING OF IMPROVEMENT	PSYCHOLOGIST GRADING TEST SCORE (23–31)	PSYCHOLOGIST GRADING BEHAVIOR (32–33)	PARENTS' REPORT	Reduced Violence and Primitivity	Increased Conformity	More Reduced, Bizarre Appropriate	Greater Anxiety	Increased Emotional Control	Increased Security	Increased Obsessive Thinking	Greater Interest in People	Reduced Fantasy	Reduced Distractability	Reduced Hyperactivity
	13	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
1	4+	++++	++++	++++	++	++++	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
48	3+	+++	+++	+++	++	++++	✓	✓	✓							✓	✓
19	3+	+++	++to +++	NT	++	++					Not Testable					✓	✓
74	2+	++to +++	++to +++	+	+	0	✓										✓
58	2+	++	++	+++	++	•		✓					✓	✓		✓	✓
73	1+to 2+	++	+	NT	++	++					Not Testable					✓	
16	1+	0 to +	+	NT	+	0					Not Testable					✓	
45	0 to 1+	+	+	0	+	0 to +				✓							

NT - Not Tested • - Unreliable

b. *Physiologic Findings:*

1. Significantly, the three patients with an average scored improvement of 3+ and 4+ "tolerated" the smallest amount of histamine, as indicated by blood pressure, both as to absolute dosage and in proportion to body weight. (Fig. 1)

2. A high tolerance to thyroid extract was exhibited by all five children administered this endocrine substance.

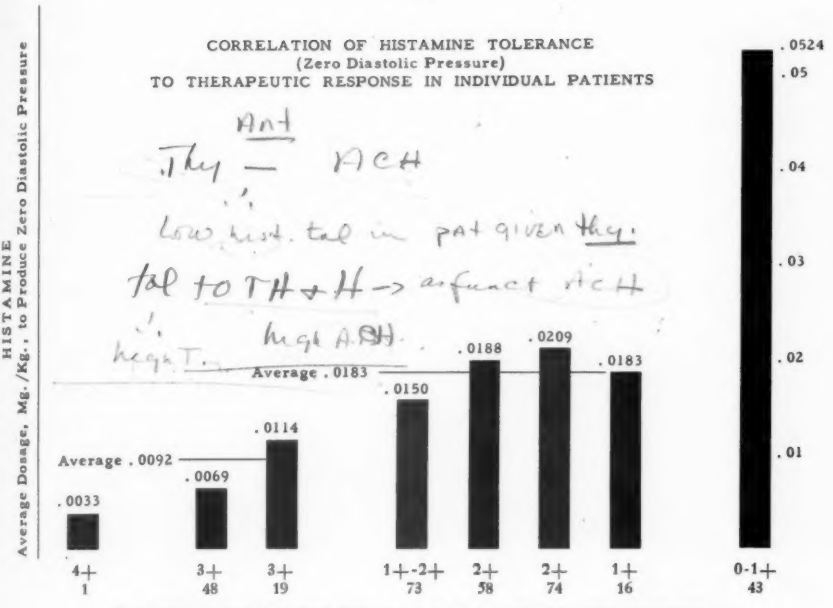
3. A high incidence of "thyroid pathology" was found in the mothers; i.e., visibly enlarged and/or palpable thyroids in four, a history of thyroidectomy in one, and a history of "thyroid trouble" in adolescence in one who was also noted to have marked hirsutism. Thyroid uptake studies revealed a tendency of hyperfunction in four and slight underactivity in two.

V. PHYSIOLOGIC FACTORS RELATING TO ETIOLOGY AND PATHOGENESIS

a. *Endogenous Neuroendocrinologic Factors:*

In earlier communications[15-24] evidence was reviewed indicating that an overative adrenocortical excess, in the presence of thyroid and/or gonadal and/or histamine deficiency, may play a rôle in the etiology and pathogenesis of the schizophrenias, which was categorized as a disorder of equilibration.

Fig. 1



b. *Findings Relating to Hormonal Dysequilibrations:*

1. Are evidences of operative adrenocortical excess also present in childhood schizophrenia? We have previously referred to indirect evidence of an antagonistic or "antidyne" relationship existing between thyroid and adrenocortical hormones as reflected in the reduction of histamine tolerance in patients given thyroid extract. If tolerance to thyroid, as to histamine, reflects, among other factors, body levels of operative adrenocortical hormone, then a high tolerance to thyroid in childhood schizophrenia could indicate high operative adrenocortical concentrations. The fact is that five children in this series who were placed on thyroid tolerated at least 3 to 5 grains (0.06 to 0.2 Gm.) of thyroid daily—actually equaling the reported tolerated dose in cretinism.

2. Is there a relationship between the severity of the disease process and tolerance to histamine? In the present study, it is interesting that prognosis was noted to show an inverse relationship to histamine tolerance—the most marked improvement being scored by the two children with the lowest tolerance, while the one with the greatest tolerance showed practically no benefit at all. When dosages per kg. of body weight are averaged on the basis of improvement, improvement is likewise shown to be inversely related to tolerance. While this is of importance prognostically, it may be of greater importance therapeutically in that it may suggest as a possible therapeutic objective the reduction of tolerance to histamine.

With regard to the relationship between histamine tolerance and severity of illness, we have previously observed a *descending order of tolerance to histamine* on the basis of both absolute dosage and dosage per kg. of body weight; namely, in:

A. Hospitalized adult schizophrenics as a group.
B. Nonhospitalized adult schizophrenics.
C. Nonhospitalized adolescent schizophrenics.
D. Nonhospitalized psychoneurotics.

Within the schizophrenic group, furthermore, correlation between the severity of the disease process and histamine tolerance has also been noted.

c. *Exogenous Endocrinologic Factors Bearing on Congenital and Hereditary Influences:*

Our neuroendocrinologic formulations suggest that both congenital and hereditary factors must be explored for evidence of hormonal influence. Congenital factors could, hypothetically, exert their influence *in utero* through placental exchange and genetic factors through the inherited endocrinologic as well as neuronal constitution. The mothers of our childhood schizophrenics showed thyroid abnormality in four out of eight cases, while thyroidectomy for "goiter" had been performed on a fifth and the sixth reported a history of "thyroid trouble" during adolescence. Thyroid function studies with radioactive iodine revealed overactivity in four and a tendency to underactivity in two of these mothers.

The finding of thyroid pathology in six of the eight mothers of childhood schizophrenics suggests a highly important link between the psychiatric process on the one hand, and an organic, more specifically, a metabolic, defect in one of the parents, on the other. This may have many broad implications bearing on the relationships among heredity, congenital factors, psychogenic forces, and endocrinologic alterations as they relate to the etiology and pathogenesis of this malignant psychosis. It points important clues that may help explain the sex differential in schizophrenia with the advance in the life cycle; it may help define the maternal contribution *in utero* and sharpen some of the statistical data relating to both probands and siblings.

We have not only noted thyroid enlargement in some mothers of childhood schizophrenics; we have also found it in the so-called "nonpsychotic" siblings and, not infrequently, in some of the patients themselves.

Here, Kraepelin's clinical acuity has this to offer: "In a series of cases, I observed diffuse enlargements of the thyroid gland, *occasionally the disappearance of such enlargements immediately before the first appearance of morbid phenomena,* also *repeated rapid change in the size of the gland during the development of the malady*" (emphasis added).[25] However, the high incidence of thyroid disease in Germany at the time deterred him from inferring an etiologic and pathogenetic relationship between thyroid enlargement and dementia praecox. "Nevertheless," Kraepelin continues, "the general statement may perhaps with all reserve be made, that a series of facts in dementia praecox make probable up to a certain degree the existence of an auto-intoxication in consequence of a disorder of metabolism."[25] Certain of Kraepelin's contemporaries did accept a causal relationship between

thyroid dysfunction and dementia praecox: Lundborg,[25] who in addition suggested a parathyroid implication; and Blum,[25] who claimed similarities to catatonia in the behavior of thyroidectomized dogs. Pavlov[26] later demonstrated behavioral changes in thyroidectomized dogs and also in castrated animals.

VI. CLINICAL FINDINGS RELATING TO ETIOLOGY AND PATHOGENESIS

a. *Age of Onset:*

Onset occurred before the age of 4 in all the children in our series and before the age of 2 in half of them. This corresponds with the most common periods of onset of childhood schizophrenia reported by others. Bradley[27] gives 3 to 4½ years as the most common period of onset, while Bender indicates that the largest single group showed initial symptoms during the first two years of life.

Of interest in relation to the age of onset in childhood schizophrenia are the historic clinical designations—*Dementia praecoccissima* and *Dementia infantilis*.

Dementia praecoccissima was described by de Sanctis[28] as occurring as early as the third year of life, while Weygandt[29] in 1908 referred to *Dementia infantilis* in prepubertal patients. Heller,[30] in the same year, also categorized six children as having *Dementia infantilis*, with onset during the third and fourth year. Weygandt[29] differentiated sharply between *Dementia infantilis* and idiocy. Kraepelin,[25] however, took issue with him. "Long ago," he wrote, "I brought forward the hypothesis that certain not exactly frequent forms of idiocy with developed mannerisms and stereotypes might be early cases of dementia praecox." In 1921 Zappert,[31] expanding on *Dementia infantilis*, referred to its most frequent origin as falling into the third to the fourth year. It is thus evident that some of the gross clinical manifestations of the schizophrenic process are recognizable before the second year, with the onset in most patients apparently antedating the fourth year.

b. *Incidence:*

Schizophrenia in the first decade of life has been termed "rare"; yet Kraepelin traced the onset of the disease process back to this epoch in 3.8 per cent of his cases; and Bleuler[32] "to the first years of life, in at least 5 per cent of the cases." Both believed these figures to be minimal. Thus schizophrenia appears in a significant number of individuals despite limitations in environmental trauma and the preclusion of pubertal, reproductive, and involutional disturbances.

c. *Clinical Findings Bearing on Heredity:*

Hereditary factors are seen more vividly when the parents of schizophrenics can be worked up psychiatrically and psychologically. Clinical and psychological examination in the present series (to be reported subsequently) revealed that nearly all of the mothers are what may be called "latent" or, as we prefer, "compensated" schizophrenics.

The incidence of schizophrenia among parents of the schizophrenic children in this series is much higher than that noted in previous reports on parents of older schizophrenics. It is probable, however, that few of the compensated schizophrenic mothers of these children

would have been identified as such in routine anamnesis. These findings are nevertheless, in line with the observations of Despert,[33, 34] Ssucharewa,[35] Grebelskaja-Albatz,[36] and others who have reported a heavier hereditary taint in childhood schizophrenia than has been reported in adult schizophrenia. Our findings of compensated schizophrenia in nearly all of the mothers of the children of this series relate to the report of Lurie, Tietz, and Hertzman,[37] that instability is more often found in mothers than in fathers of childhood schizophrenics. Despert,[33] in writing of the parents of childhood schizophrenics, noted that "the mothers were aggressive, overanxious, oversolicitous, and exhibited a marked ambivalence to these children. . . . The father plays a very subdued rôle." Careful diagnostic study of the mothers in the present series revealed that underlying such or similar symptoms was a compensated schizophrenia.

d. *Clinical Findings Bearing on Congenital Influences:*

In view of the clinical findings of this study and our formulations on the neuroendocrinologic etiology and pathogenesis, we undertook to examine the possibility that while both parents might contribute to the process through heredity (in respect to predisposition of cerebral neurones and the character of the endocrinium), the mother might exert an immediate influence on the fetus, by virtue of the child's existence within her hormonal milieu during the critical developmental period from conception to birth.

Findings of "thyroid pathology" previously referred to were made in the mothers of these childhood schizophrenics. Gross evidence of an abnormal maternal hormonal contribution *in utero* might be inferred from the existence of abnormal thyroid function in five mothers and a suggestive history during adolescence in the sixth. The first findings were clinical (thyroid enlargement, either visible or palpable). Subsequently, radioactive iodine studies defined abnormal thyroid function and supported the clinical observation. (Data on this aspect of these investigations will be presented in full in other communications.)

That interaction between maternal and fetal hormones and endocrine glands occurs has long been known. In fact, "congenital goiter [in the newborn] has been regarded as a compensatory hypertrophy, due to the deficient function of the mother's thyroid. On the other hand, cases of athyreosis—children who are normally developed at birth but exhibit symptoms soon afterward—show that during intrauterine life the thyroid function of the child has been maintained by the maternal thyroid hormone."[38] In diabetes, conversely, the fetal pancreas may assist the mother. It becomes apparent that in all hormonal states, congenital as well as hereditary factors must be considered. It is thus suggested that maternal hormonal dysequilibration may adversely affect neurones of the fetus, "set the soil" for, and raise susceptibility to further damage. For example, an infant who may have suffered a "schizophrenia" *in utero* may, if the process is arrested at parturition, become a schizoid personality. On the other hand, if inherited or developmental (e.g., pubertal, gestational, involutional) hormonal dysequilibrations are superimposed upon the congenital damage, the same individual may develop a full-blown schizophrenic process. The thesis of a primacy of neuroendocrinological factors does not exclude the possible pathogenetic contributions of social and psychological forces. As Bleuler[32] puts it: "Psychic experiences—usually of

an unpleasant nature—can undoubtedly affect the schizophrenic symptoms. However, it is highly improbable that the disease itself is really produced by such factors. Psychic events and experiences may release the symptoms but not the disease. . . ."

A few of the findings and deductions of this report may be examined in the light of some available statistical data. If the concept of a greater maternal contribution to psychiatric disease is valid, then one would anticipate a higher incidence of frank schizophrenia in the mothers than in the fathers of schizophrenic probands. In Pollack, Malzberg, and Fuller's[39] studies of dementia praecox and manic-depressive patients admitted to Utica State Hospital during the three years from 1928 to 1930 both male and female probands revealed a *higher incidence of known mental disease in mothers than in fathers,* in absolute numbers. This was even more striking when the absolute numbers were compared to expected rates. (Table 3)

Table 3

Incidence of Mental Disease in Mothers and Fathers of Schizophrenic Probands.
From Pollack, Malzberg and Fuller[39]

	MALE				FEMALE				MALE AND FEMALE			
PROBAND	Number Known Histories	Expected Cases Mental Disease	Actual Known Cases Mental Disease	Anticipated Cases	Number Known Histories	Expected Cases Mental Disease	Actual Known Cases Mental Disease	Anticipated Cases	Number Known Histories	Expected Cases Mental Disease	Actual Known Cases Mental Disease	Anticipated Cases
FATHER	92	3.7	2		82	3.3	2	1.0	174	7.0	4	2.4
MOTHER	92	3.2	7		82	2.9	6	1.3	174	6.1	13	2.8

	MALE				FEMALE				MALE AND FEMALE			
PROBAND	Number Known Histories	Expected Cases Mental Disease	Actual Known Cases Mental Disease	Anticipated Cases	Number Known Histories	Expected Cases Mental Disease	Actual Known Cases Mental Disease	Anticipated Cases	Number Known Histories	Expected Cases Mental Disease	Actual Known Cases Mental Disease	Anticipated Cases
FATHER	59	2.4	0	0.8	95	3.8	3	0.8	154	6.2	3	1.6
MOTHER	59	2.1	2	0.9	95	3.3	4	0.9	154	5.4	6	1.8

Further, one would anticipate a higher incidence of schizophrenia in the children of schizophrenic mothers as compared to fathers. Kallman's[40] figures do not bear this out. However, in the case material of Pollack, Malzberg, and Fuller "no selection was exercised in the choice of patients, other than that arising from the existence of a well-defined psychosis." On the other hand, Kallman's "omission of schizophrenias that struck us as symptomatic, and all cases associated with lues and alcoholism, naturally brought about a greater reduction of pure schizophrenia in the number of male cases than of female so that in the end we had 647 female as against only 440 male probands." Thus these two studies are not comparable.

The data of Koller's study,[41] reported in 1895, in which tainting was compared in the families of 370 "mentally sound" individuals and 370 patients (150 men and 220 women) admitted to Burghölzli in 1885 and 1886 appear to be in line with Pollack, Malzberg, and Fuller's findings as to parents of probands. The findings of "mental disease" *in mental patients' mothers almost double those in the fathers.* (Table 4)

Table 4

Tainting in Families of "Mentally Healthy" Compared to "Mentally Diseased" From Koller[41]

	MENTALLY HEALTHY											MENTALLY DISEASED										
	Suicide	Mental disease	Nervous disease	Eccentricity	Dementia senilis	Apoplexy	Alcoholism	Total Factors		Factors per each of the 370 healthy individuals	Factors per each of the 218 healthy with taints	Suicide	Mental disease	Nervous disease	Eccentricity	Dementia senilis	Apoplexy	Alcoholism	Total Factors		Factors per each of 370 patients	Factors per each of 284 tainted patients
								Number	Per cent										Number	Per cent		
Father	2	7	11	14	....	16	30	80	16.6	0.2	0.4	4	24	9	42	4	19	55	157	28.5	0.4	0.6
Mother	....	10	29	8	1	13	2	63	13.2	0.2	0.3	....	44	16	25	6	11	8	110	20.0	0.3	0.4
Grandparents	....	12	6	9	15	40	21	103	21.6	0.3	0.5	1	20	1	7	3	12	8	52	9.4	0.1	0.2
Siblings	2	27	28	14	....	3	16	90	18.9	0.2	0.4	2	68	22	21	....	4	18	135	24.5	0.4	0.5
Uncles and aunts	6	26	19	16	....	25	26	141	29.6	0.4	0.6	7	41	8	10	2	7	22	97	17.6	0.3	0.3
Total	10	94	93	61	16	97	107	477	100.0	1.3	2.2	14	197	56	105	15	53	111	551	100.0	1.5	1.9

e. *Sex:*

The ratio of males to females in this series was 5:3. Bradley, who totaled the cases of Grunthal,[42] Grebelskaja-Albatz,[36] and Lutz,[2] found 72 boys to 24 girls. Bender[1] reported 70 boys to 28 girls.

Table 5

Age of Onset of Schizophrenia in 618 Patients (in Percentages) From Wolfsohn[43]

AGE OF ONSET OF ILLNESS	MEN *	WOMEN *	TOTAL *
1 - 15	6	3	4
15 - 20	21	16	18
20 - 25	25	20	22
25 - 30	22	18	20
30 - 35	10	14	12
35 - 40	10	11	11
40 - 45	5	5	5
45 - 50	4	6	4
50 - 55	0	5	3
55 - 60	0	2	1
60 - 65	0	0	0

* Figures in percentages

The higher incidence of childhood schizophrenia in males as compared to females is suggestive in the light of our fundamental neuroendocrinologic formulations. Within the frame of reference of Freudian psychodynamics and the social structure of our society, one would not anticipate an incidence of childhood schizophrenia of 2:1 or almost 3:1 in males as compared to females, if psychogenicity were the determining factor. While genetics seems to play an important rôle, it could not by itself account for this sex ratio, especially since the incidence of schizophrenia in the female approaches that in the male with the passage of years. This latter observation is supported by Wolfsohn's[43] data on the onset of schizophrenia in 618 patients at Burghölzli. (Table 5)

All these data appear more comprehensible in the light of the formulations that hormonal dysequilibrations are primary factors in the etiology and pathogenesis of major psychiatric disorders.

Assuming equal hereditary tainting for males and females, a number of significant endocrinologic events may then be correlated with the changing sex incidence at different periods of life.

In utero, both the male and female fetus are exposed to the hormonal equilibrations and dysequilibrations of the mother. The male child, however, may have to contend with a greater hormonal problem, because of the sex difference between himself and his host. It would thus seem that the cerebral neurones of the male may be more exposed to damage. The sex difference in childhood schizophrenia may be but one manifestation of this difference. Boys are popularly considered more difficult children to handle, are more restless and "mature later" than girls. These factors have been termed manifestations of "personality differences," but is not personality a resultant of neuronal status and hormonal effects on cerebral function, as well as of other factors?

Our thesis that the schizophrenic process may, in many individuals, start *in utero* may lead to a number of interesting deductions. Let us consider a postulated congenital cerebral damage as the stratum upon which subsequent events may be predicated. Given continuing hormonal dysequilibrations due to the inherited endocrinium in certain patients, the result may be childhood schizophrenia—more common in males than females perhaps because of greater predisposing neuronal damage *in utero*. Assuming, on the other hand, no further major hormonal damage postnatally, then one might consider schizoid personality and other "eccentricities" as *in utero* schizophrenia "arrested at parturition" or as "arrested cerebral damage." One should then anticipate a higher incidence of such disorders as "eccentricities," schizoid personalities and perhaps alcoholism in males as compared to females.

Alcoholism is, of course, known to be predominantly—but not exclusively—an affliction of males. Koller's[41] data are interesting in regard to both "eccentricity" and alcoholism in that they show the incidence to be (1) higher for males (this is diametrically opposite to his findings for "mental disease"); and (2) also higher for fathers of schizophrenics as compared with mothers. The parents of "mentally diseased" patients in all categories are more frequently afflicted than those of normal persons.

If one were to consider schizophrenia in the male as an indication, to a certain degree,

of a greater contribution by the mother to the individual schizophrenic process, one would anticipate a higher incidence of schizophrenia in the siblings of male schizophrenics. The findings of Pollack, Malzberg, and Fuller are in line with this deduction. They state: "There appears to be a tendency for relatively more tainting in the families of the male probands. In view of the small total, however, the results can be considered only suggestive. Thus, among the siblings of the male probands there was an excess of 86.6 per cent of the corrected total of mentally-diseased over the expected total, whereas, among the siblings of the female probands the corresponding excess was only 55.1 per cent."

At puberty both sexes are exposed to hormonal vicissitudes, as pituitary stimulation brings into play adrenocorticotropic, gonadotropic, thyrotropic and other hormones in varying balances. Subsequently the more marked hormonal variations in the female may make a greater contribution to cerebral damage. As a result, the incidence of schizophrenia in adolescent females begins to approach that of males. Continuing cyclical shifts and the subsequently superimposed hormonal changes of pregnancy and parturition tend to bring the incidence still closer until ultimately, in the climacterium, cases of schizophrenia in females may outnumber those in males.

It would seem, therefore, that a neuroendocrinologic approach may help explain differences in the manifestation of schizophrenia in respect to age, sex and maternal influences.

Whatever the ultimate fate of this thesis and the deductions made from it, it is hoped that they will stimulate investigation directed toward the further clarification of the etiology and pathogenesis of schizophrenia.

SUMMARY AND CONCLUSIONS

Investigation of the schizophrenias of childhood is valuable because hereditary influences are more accesible to examination and evaluation and because maternal contributions *in utero* are temporally less remote and both are less complicated by environmental and somatic factors.

The present report has reviewed the following:

1. Observations on eight childhood schizophrenics treated with histamine over a three-month period. Five were male, three female. Five of the patients had previously been treated elsewhere with ECT, with temporary improvement reported in four and no change in one.

2. In this histamine-treated series, clinical improvement was recorded as an average of ratings by the psychiatrist, the nurse, the psychologist, and the parent. The results revealed:

Grade	*No. of Patients*
4+	1
3+	2
2+	3
1+	1
0	1

3. Three patients, in the 9-year age group, scored 3+ and 4+ improvements. The im-

portance of approaching puberty in those patients who responded best to therapy was taken into account and discussed neuroendocrinologically.

4. Significantly, the patients evidencing best response "tolerated" the least amount of histamine as indicated by blood pressure.

5. A high tolerance to thyroid hormone was exhibited by all children.

6. A high incidence of thyroid pathology was found in the mothers of the children.

7. A high incidence of compensated schizophrenia was observed in the mothers.

8. The possibility of an *in utero* neuroendocrinologic contribution to the etiology and pathogenesis of schizophrenia is posed.

9. The significance of the age of onset and the changing sex ratio of male to female schizophrenics is raised and discussed.

10. The findings are interpreted in the light of a physiodynamic neuroendocrinologic formulation suggesting that operative adrenocortical excess is related to the etiology and pathogenesis of schizophrenia. In this light, alterations in thyroid physiology and thyroid pathology may reflect the results of compensatory attempts to counter the operative adrenocortical excess.

Histamine biochemotherapy has opened new approaches both to the treatment of the schizophrenias of childhood and to the investigation of the etiology and pathogenesis of this disorder of equilibration.

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The present volume of the *Journal of Clinical and Experimental Psychopathology* is dedicated to the memory of Dr. van Ophuijsen and will present, during the course of 1951, reports of researches which he initiated, in which he participated, or which were in the process of completion at the time of his death, May, 31, 1950.

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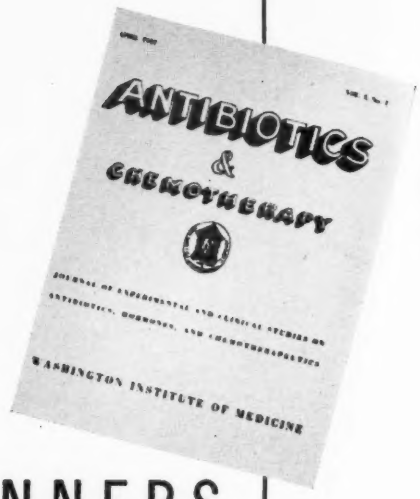

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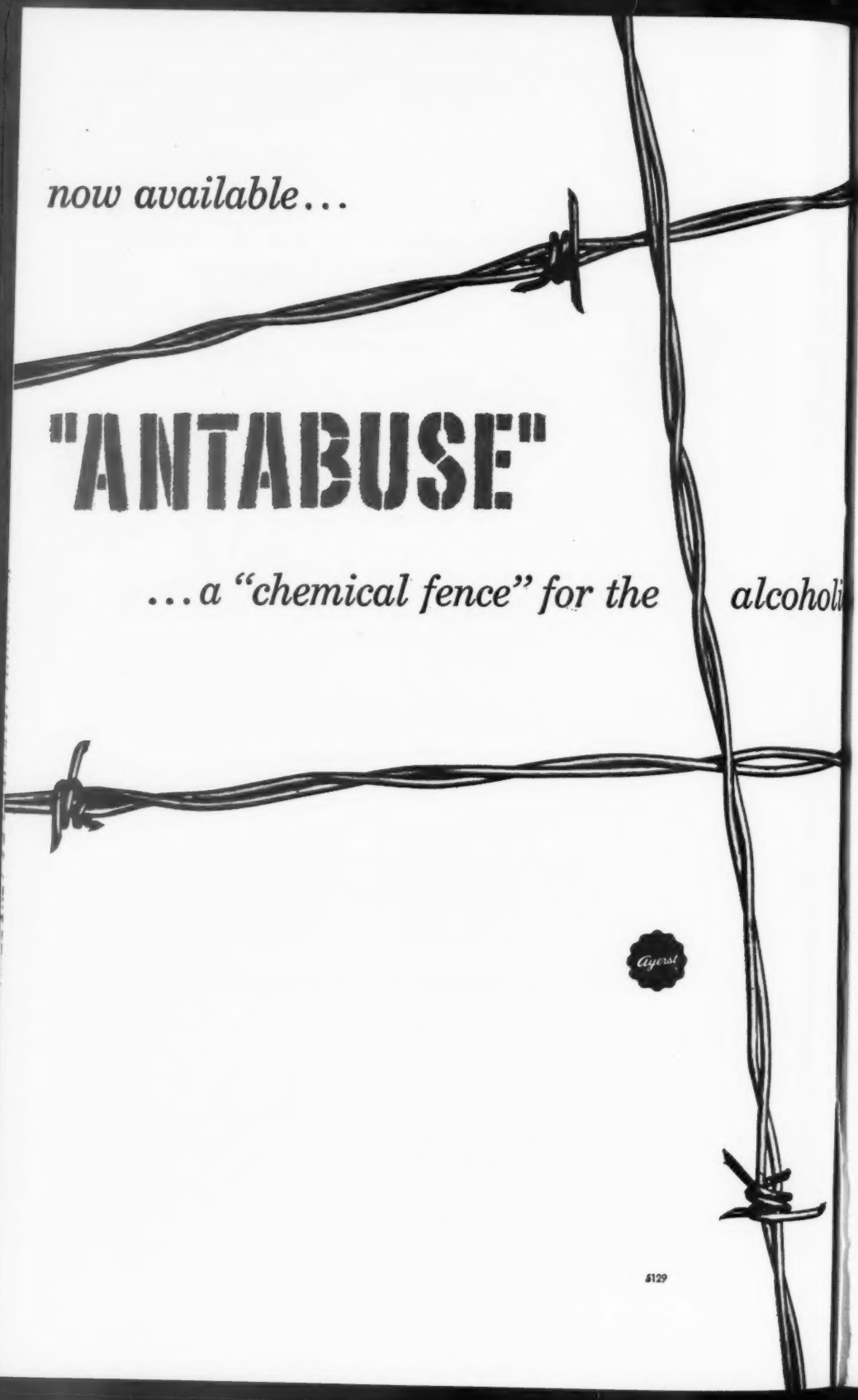

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OBITUARY

Dr. Vernon C. Branham

Dr. Vernon C. Branham died in Washington, D. C., on October 23, 1951. He was active in his duties until October 22nd as Chief of Out-patient Section of the Division of Psychiatry and Neurology, Central Office, Veterans Administration, Washington, D. C.

He was born May 26, 1889, in Denver, Colorado. Educated in the schools of Denver, he received his Bachelor of Arts from the University of Colorado in 1913. During the following two years, he did graduate work in chemistry, receiving a Master of Science degree from the University of Denver in 1914, and a Master of Arts from Columbia University, New York City in 1915. He then entered medical school and received his doctorate in 1919 from the University of Colorado. Following his graduation from medical school, he served a one-year internship at St. Elizabeth's Hospital in Washington, D. C. where his interest in psychiatry became established under the influence of Dr. William Alanson White. He then joined the out-patient department staff of the Cornell Medical School where he served until 1923 when he became superintendent of the Institute for Male Delinquents, Napanoch, New York. His activities for the next twenty-seven years centered about the care of the defective delinquent and furthering mental hygiene programs. In the ten years from 1924 to 1934 he was, in turn, director of the State Commission for Mental Defectives, director of State and New York City Commission for Mental Hygiene and then deputy commissioner of correction for New York State in charge of the psychiatric service for the prisons. He was appointed superintendent of Woodbourne Institute for Defective Delinquents in 1935 and remained in this capacity until 1947. During the past four years, he engaged untiringly in the development of the Veterans Administration mental hygiene clinics throughout the country.

While superintendent of the Woodbourne Institute for the Defective Delinquent, he recognized the need for a publication which would collect the observations and thinking of those in the profession who were assuming the responsibility of care and treatment of the individual whose behavior presented a social problem. As a result, he published and edited "The Journal of Criminal Psychopathology." Later he widened the scope of the material of his original publication and changed it to the "Journal of Clinical Psychopathology." He wrote a treatise on "The Classification and Treatment of Defective Delinquents" and other articles allied to this subject. In 1949, he edited with Samual Kutash, Ph.D. the "Encyclopedia of Criminology."

He was a man of quiet, easy manner which belied the dynamic force of character and abilities which made him so effective a pioneer. He was always alert to the needs of his program and flexible in adopting procedures to enhance their effectiveness. He will always be remembered by his friendly smile and soft-spoken greeting by those who knew him as well as his persistent effort to assist those who were his associates.

JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY

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The First van Ophuijsen Memorial Lecture

Some Recent Advances In Cellular Chemistry and Physiology

by Professor Hans Lettré

THE INSTITUTE FOR EXPERIMENTAL CANCER RESEARCH, UNIVERSITY OF HEIDELBERG. THE CREEDMOOR INSTITUTE FOR PSYCHOBIOLOGIC STUDIES, CREEDMOOR STATE HOSPITAL, QUEENS VILLAGE, N. Y.

May I first of all express my gratitude for the honor that has been conferred on me in choosing me to deliver the First van Ophuijsen Memorial Lecture. It may seem strange to you that a biochemist who deals primarily with experimental cancer research has been called upon to speak in honor of a man whose interests were focused in the field of psychiatry and the nervous system; but Dr. van Ophuijsen always emphasized the physiologic basis of psychiatric disorders; and it is a fact that in cancer research as in psychiatry we deal with the cell as the ultimate unit. Since the potential of morphologic methodology is limited, it is always necessary to seek recourse with biochemical methods—a field which we designate today as cytobiochemistry.

In the year 1940 the German pathologist, Dietrich, formulated the task of chemistry in cancer research in these terms: "One hundred years ago the microscope attacked cancer as a problem in morphology, tracing it down into the ultimate intricacies of cell and tissue changes. Where the resolving power of the microscope ceases, biochemistry begins its task of opening up the infinitely minute structure of living matter." True, today the electron phase contrast microscopes have pushed back the limits of morphological cell investigation. Yet the "chemical microscope" maintains its importance, for its resolving power reaches down into the molecular realm, permitting analysis not only of the structure but of

Presented at the Second Creedmoor Conference, Creedmoor Institute for Psychobiologic Studies, Creedmoor State Hospital, New York, October 2, 1951.

the functions of cell components. Its possibilities have not yet been fully exploited, and my remarks represent but an outline, utilizing a very low degree of magnification. I hope you will agree that the same considerations apply in some degree to psychiatry.

The cancer cell is a cell characterized by constant growth but without function; the nerve cell, on the other hand, is characterized by a steady state of function, but without growth. Thus these two cell types appear as the two extremes of cellular behavior. A comparison of cancer and nerve cells therefore is of interest for both the cancer specialist and the psychiatrist.

To begin with the cancer cell—we must first define what we mean by growth. Growth is augmentation of living substance. Since, unlike a crystal, a cell cannot increase its size beyond a certain limit, the process of augmentation involves cell division. Hence the growth of biological systems is inconceivable without cell division. The process of growth itself must be divided into two phases. The first of these is the state of preparedness for cell division; the second is cell division itself.

The first phase embraces the doubling of all the essential components within the cell-proteins, nucleic acids, lipids, structural elements such as mitochondria, the material that goes into the structure of the chromosomes. In this first phase of growth the environment of the cell is of equal importance with its metabolism, and thus cell nutrition takes on great importance. Even with cells exhibiting extremely swift growth, the first phase consumes approximately twenty times as much time as the second-cell division proper. It seems probable that this second phase is not nearly so dependent on extracellular as it is on intracellular factors such as metabolism.

According to the findings by Otto Warburg, some twenty-five years ago, there is an interrelation between metabolism and growth. He summarized his result in these words: "No growth without glycolysis." In mature tissue in a state of rest, respiration predominates over glycolysis; in embryonic tissue glycolysis reaches a magnitude comparable with that of respiration; and in malignant tissue glycolysis predominates over respiration. It has not heretofore been possible to give a satisfactory explanation of these findings, and thus it would seem to be of some significance to determine whether the aforementioned metabolic interdependence applies primarily to the first or the second phase of growth.

In our own investigations we therefore turned to the question of whether growth inhibitors affect metabolism as a whole or glycolysis and respiration separately. We found that the inhibition of glycolysis inhibits growth as a whole to a greater degree than does the inhibition of respiration. There are, however, other growth inhibitors that fail to affect cell metabolism at all — neither its respiratory nor its glycolytic aspects; among these are the so-called mitotic poisons.

In the course of these inquiries we came across a surprising result. It has long been known that fibroblasts may be grown in tissue cultures under aerobic as well as anaerobic conditions. We were studying cell behavior during the transition from aerobic to anaerobic conditions; and we observed that this caused movements of the cell surface similar to those usually observed in the suppression of respiration by means of poisons under aerobic conditions. These movements of the cell surface persisted for one hour; and the cells

regained their normal spindle shape only at the end of three hours. This means that in the transition from respiration to glycolysis the cell requires several hours to adapt itself. Our studies with respiratory poisons revealed that in this process compounds with energy-rich phosphate bonds are of special importance — for example, adenosine-triphosphoric acid. During respiration twelve molecules of ATP are synthesized in carbohydrate metabolism per molecule of hexose, while in glycolysis the number of molecules is only two. Thus a transition from aerobic to anaerobic conditions, or respiratory intoxication, involves a breakdown of the ATP level of the cell. Calculations in connection with oxygen uptake and glucose consumption reveal that a tissue culture of fibroblasts synthesizes less than 100 micrograms of ATP per hour during respiration. Since ATP is extremely unstable, we must add to the medium of a tissue culture a substantially greater amount than that calculated theoretically whenever we wish to make up for the missing product of respiration. We do indeed observe in respiratory intoxication that when 1,000 micrograms of ATP are added, no movement of the cell surface takes place. This experiment enables us to explain the movements and changes in shape in the cell surface if we use, as a basis for comparison, Szent-Györgyi's experiments with the contractile proteins of muscle. Szent-Györgyi extracted the so-called actomyosine which can be converted into fiber form. Such fibers contract whenever ATP is added and relax when it is removed. Assuming that the cell surface contains an actomyosine-like protein, its given state of tension is dependent on the ATP level of the cell. If respiration has created a high ATP level, the surface is necessarily in a state of contraction; whereas, conversely, in a breakdown of the ATP level the cell surface relaxes and contracts only intermittently. It is this latter alternation of relaxation and contraction that accounts for the changes in cell shape and the movement of the cell surface. This approach gives rise to the view that a cell in a so-called "state of rest" is actually performing a significant amount of work, because of its state of contraction; on the other hand, a cell whose surface is in motion shows a smaller chemical energy output, on account of its state of relaxation.

From the morphological point of view we may compare cells in which respiration is in a state of intoxication with those that are in the process of cell division. In all likelihood we may also infer a chemical resemblance — in other words, a cell in the process of division may be in a state of suppressed respiration. This agrees well with certain findings by O'Connor who made a quantitative comparison between cell division and aerobic glycolysis in embryonic tissue. He found a high degree of linear correlation between the two factors — a high rate of cell division accompanied by a high rate of glycolysis, and vice versa. Yet when he extrapolated his curve to the zero point of cell division, there remained a residue of aerobic glycolysis. Thus, if we return to Warburg's line of inquiry — "no growth without glycolysis" — we may certainly assert that the second phase of growth — actual cell division — is closely associated with glycolysis; whereas the first phase of growth — preparedness for cell division — is associated with only a residual amount of glycolysis.

Our further interest lay in the question of whether cell division is possible with respiration fully maintained, and/or in the presence of the products of respiration, such as ATP.

We therefore added large quantities of ATP to the medium of tissue culture of fibroblasts growing under aerobic conditions and observed that here, too, both mitosis and cell division took place. But while the behavior of the chromosomes showed no deviation from the cell without added ATP, cell shape and movements of cell surface were altogether different. The cells remained spindle-shaped even in mitosis, and neither relaxation nor surface movement was observed. Actual cell division, moreover, took place by rupture rather than by central constriction. This type of cell division could not take place under normal conditions, but only in the presence of this artificially created high ATP level. In normal cell division, relaxation of the cell surface facilitates division by constriction. In fact, this seems to be the purpose of the transition from respiration to glycolysis. You may perhaps visualize the situation in terms of a tightly inflated balloon, which would be difficult to subdivide into two sections, while one less tightly inflated would be more amenable to such subdivision. This comparison, of course, is scientifically inaccurate, since no actual diminution of cell contents is involved.

The fact that cell division is possible in the presence of a high ATP level shows on the other hand that other contractile systems requiring ATP must be present in the normal cell. This, in turn, agrees with our own findings that contractions of the cell spindle require ATP. Colchicine, a mitotic poison, inhibits spindle contraction and possibly even spindle formation. We found that ATP can actually cancel out the inhibitory effect of colchicine; and creatine-phosphoric acid also displays an antagonistic effect toward combinations of colchicine with certain synergists. ATP and creatine-phosphoric acid are the energy sources of muscle contractions; and our findings therefore would seem to support a parallel between spindle contraction and muscle contraction. Our investigations can lay no claim to having fully elucidated the mechanism by means of which colchicine is effective. Murray, de Lam, and Chargaff found that meso-inositol exerted a specific inhibitory effect on colchicine and suggest the possibility that meso-inositol is one of the building bricks of the cell spindle. Their experiments, in other words, suggest that colchicine interferes with the formation rather than the function of the cell spindle.

If we now summarize the preceding consideration, we may say that growth is possible with respiration alone (without glycolysis) and with glycolysis alone (without respiration). But when we take into account the two phases of growth, glycolysis appears to be rather rigidly coupled to the second. The first phase proceeds under respiration with better utilization of cell energy, although it is also possible with glycolysis alone. O'Connor's results show that a residual amount of glycolysis may be associated with the first phase of growth; and here an important phase of the problem remains to be elucidated.

The cancer cell displays all the characteristics of growth — a swift increment of all the essential cell components, with resulting cell division. Its antithesis, the nerve cell, never displays cell division in the adult organism; its function is manifestly purely regulatory and integrating. The question arises whether it displays any evidence of growth at all. Experiments by Paul Weiss in this country have shown that a constant process of regeneration takes place at the axone endings and that this new material is projected outward from the cell nucleus at a rate of about 1 mm. per day. Thus the actual rate of formation of

new cytoplasm is very considerable, and if we were to define growth as increment in mass, the nerve cell effects such growth at the same rate as the tumor cell. But here it is purely a specialized case of increase of cytoplasmic material, without simultaneous increase in nuclear material. Investigations by Caspersson and his disciple Hydén in Sweden and by Oskar Vogt in Germany have shown a special involvement of the nucleolus. The nucleolus in a healthy nerve cell is greatly enlarged; indeed, according to Vogt, the behavior of the nucleolus as evidenced by its responsiveness to staining is an index to the health of a nerve cell. This view closely coincides with Caspersson's findings that the nucleolus plays an important part in the proliferation of cytoplasmic material. The behavior of the cell as a whole is therefore strongly dependent on the behavior of this organella. By and large, the behavior of a given type of cell in a state of function is characterized by the fact that one of its organelles comes to the fore in cell metabolism. It is true that this involves the production of substance which is quantitatively comparable with the process of growth, yet actually not all cell components share in the increment and the process therefore does *not* represent true growth. In its interaction with the environment, however, this type of mass augmentation is just as dependent on the conditions of that environment — such as nutrition — as is the first phase in the growth of dividing cells.

It may be of historical interest that the first tissue culture to be grown by Harrison in 1908 (in this country, by the way) consisted of nerve cells. Unfortunately, little use has been made of this technique of studying nerve tissue under the influence of a varying environment. More recently Pomerat has confirmed the high sensitivity of nerve cells to the barbiturates by means of this method. Variations in the hormonal aspects of the environment are bound to be of special significance with respect to nerve tissue cultures. Our own experiments were aimed primarily at the problem of cell division. Hence we worked for the most part with fibroblasts, epithelial cells, carcinomatous tissue, and bone marrow, using only a limited amount of nerve tissue; yet it is of interest that with these cell types, too, we were able to establish a high degree of dependence on the hormone make-up of the environment. Thus we found adrenalin, adreno-chrome, and estrogen hormones to exert a mitosis-inhibiting effect, whereas the adrenal cortical hormones of themselves appeared to leave cell division unaffected, though in combination with colchicine they provided a synergistic effect. This would seem to indicate that adrenal cortical hormones modify cell metabolism in the direction of paving the way for an enhancement of the effect of colchicine — just as we were able to show earlier in the case of the effects of the poisons of phosphorylation. Recent biochemical findings have shown that hormones must be looked upon as regulators and modifiers of enzyme processes. It is apparent that the study of tissue cultures may furnish important clues to the mechanisms of hormone effects.*

Permit me, in conclusion, to report briefly on another aspect of our cancer research that

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**Note:* A time-acceleration film showing: (1) the growth of fibroblasts in tissue culture; (2) mitosis of fibroblasts under normal conditions; and (3) mitosis of fibroblasts under addition of colchicine or acriflavin has been prepared under the personal direction of Dr. Lettré. The film, No. C-599, is available from the *Institut für Film und Bild in Wissenschaft und Forschung*, Bunsenstrasse 10, Goettingen, Germany.

may likewise have a bearing on the study of nerve cells. Since 1949 I have been engaged in a study of the behavior of tumor cell components in transplantation. We succeeded, in the course of these investigations, in perfecting a method by which tumor cells could be freed of their mitochondria. Repeated swelling in hypotonic solutions extrudes these cell components from their matrix, and centrifuging separates them fully. Such granule-free cells are no longer capable of growth after transplantation. They no longer engender new tumors. But when either the separated mitochondria or homogenates of intact tumor cells of the same type are added, the granule-free cells regain their capacity to engender tumors on transplantation. This means that a reconstitution of the granule-free cells and the mitochondria takes place. By and large, these investigations permit us to conclude that there are three stages of cell injury. The first is one from which the cell is able to recover by itself; the second is one from which it can recover only when cell components from undamaged cells are added; and the third represents an irreversible degree of damage from which the cell can recover neither by itself nor with the aid of added cell components. These findings resulted from our investigation of the degree to which cancer cells must be damaged to forfeit their capacity to engender new tumors. They appear, however, to be significant in the study of normal cells that have suffered varying degrees of damage. Our main interest, up to this point, naturally lay in the direction of studying the manner in which nutritives, vitamins and hormones, affected the cell environment and thus the cell. Now the important question of the effect of adding cell components has been raised — a question that may well be of significance in studying the recovery of normal cells from damage suffered.

Ladies and gentlemen, I have endeavored, in this brief review, to outline for you certain recent findings in cellular biochemistry and physiology. The brief space of time at my disposal prevents me from going into greater detail and elaborating fully the facts and implications of these findings. I hope that I have demonstrated that the methods and procedures that have been fruitful in the study of growth and cell division may be equally useful in the study of nerve cells; and that the problems posed in these two fields bear more than a passing resemblance to each other.

Hans Lettré, Ph.D.

DIRECTOR OF THE CANCER RESEARCH INSTITUTE, UNIVERSITY OF HEIDELBERG

CONSULTANT IN CYTOBIOCHEMISTRY, CREEDMOOR INSTITUTE FOR PSYCHOBIOLOGIC STUDIES

Professor Hans Lettré, First van Ophuijsen Memorial Lecturer, has achieved international recognition for his brilliant fundamental work in cellular chemistry and physiology. Son of

an engineer, Professor Lettré first took up the study of mathematics at the University of Munich in 1927. His interest then turned to chemistry and in 1932 he took his doctor's degree in this field at the University of Goettingen, where he was appointed an instructor. From 1939 to 1942 he headed the chemistry department at the Rudolf Virchow Hospital's Cancer Institute in Berlin; and from 1942 to 1948 he was Professor Extraordinary of Organic Chemistry at the University of Goettingen. Since 1948 Professor Lettré has been Director of the Institute for Experimental Cancer Research at the University of Heidelberg. From 1939 to date, he has been the author of 133 papers.

In 1950, Professor Lettré was awarded the All-German Prize in Chemistry. This year he has participated by invitation in the Gordon Research Conference on Cancer, under the sponsorship of the American Association for the Advancement of Science, and in the World Chemical Conclave. He has been a guest lecturer at the National Institutes of Health, Bethesda, Maryland; the Department of Cancer Research at the University of Wisconsin; the Ben May Laboratories for Cancer Research and the University of Chicago; the Strong Memorial Hospital and the University of Rochester; and the Tufts College Medical School. Professor Lettré has recently been appointed Consultant in Cytobiochemistry of The Creedmoor Institute for Psychobiologic Studies.

A Program for the Treatment of Psychosis With Cerebral Arteriosclerosis, With Special Emphasis on the Intravenous Administration of Histamine and Nicotinic Acid—A Preliminary Report of 29 Cases

Donald F. Moore, M.D., F.A.P.A., Charles W. Morris, M.D., Frank V. Smith, Jr., M.D., and Joe L. Lawson, Jr. Ph.D.

UNIVERSITY OF LOUISVILLE, SCHOOL OF MEDICINE

It has been said that the major problem of modern medicine is the care of the increasing numbers of aging people. The psychoses associated with organic brain diseases are prominent in this age group, both because of their frequency and their severity.

We have worked out a pilot program which seems, at least temporarily, to be capable of arresting most of these cases. Although many of the details of the physiological reactions need further study, and a series of control cases would be desirable, the program as used has relieved psychosis, and reduced morbidity and the need for hospitalization in such a high proportion of cases, that we believe this pilot study is worth reporting now.

This program is really a total push program for psychosis with organic brain disease and involves the judicious use of five types of therapy. These are:

1. Daily intravenous histamine-nicotinic acid injections.
2. Group occupational recreational therapy.
3. Individual and group psychotherapy.
4. Electric shock therapy.
5. Persistent case work therapy with the relatives of the patient.

There are many independent studies of the therapeutic effect of histamine and of nicotinic acid in the varieties of medical and psychiatric conditions;[2-27] however, the use of a combination of alternate intravenous treatments of histamine and nicotinic acid in the treatment of cerebral arteriosclerosis has not previously been reported. This element of the program will therefore be given in detail. The other four components are, in general, familiar to most physicians and will be discussed only as they relate to this particular therapeutic program.

We have been convinced that intravenous histamine-nicotinic acid therapy is of outstanding value with these psychoses and we had hoped to report on its use alone, but in dealing with patients one seldom arbitrarily avoids other therapies when they are indicated. Consequently we are presenting an integrated therapeutic program rather than an evaluation of histamine-nicotinic acid alone. There are times when each element of the program may be needed by the patient, and for maximum benefit all five elements frequently must be utilized.

From the Neuropsychiatric Service, Louisville Veterans Administration Hospital. Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

SELECTION OF PATIENTS

All patients treated were from the medical, surgical, or psychiatric service of a Veterans Administration general hospital of 1,000 beds. Some had been in the hospital for as much as 15 months; others were seen on admission, and treatment was started within a week or ten days of hospitalization. All were psychotic or had had recent psychotic episodes.

A constellation of psychiatric and neurological symptoms, usually attributed to organic brain disease, was used as a standard by which to select patients for this treatment program. All patients selected had at least one of the following psychiatric symptoms:

1. Episodes of forgetfulness and memory defect, particularly for recent events.
2. Confusion and disorientation or episodes of confusion and disorientation.
3. Loss of intellectual capacity, slowing of thinking, history of inability to maintain previous efficiency.
4. Emotional lability and mild secondary mood swings, usually depressive.
5. Diminution in ability to test reality, with a tendency to develop delusional and paranoid trends and, in several cases, actual hallucinations and delusions.

Many of the patients also demonstrated some of the following neurological findings:

1. Transient or permanent neurological changes such as focal paralyses, or anesthesias, disturbance in motor coordination, partial or complete aphasias or apraxias with history of cerebral thrombosis.
2. Positive snout, sucking, and Babinski reflexes. Evidences of involvement of the extrapyramidal system.
3. Episodes of dizziness or loss of consciousness with subjective symptoms of ringing in the ears and headaches.
4. Other evidences of hypertension or arteriosclerosis in the eye ground and peripheral circulation.

CLEARANCE PROCEDURES

1. *The patient is examined and interviewed by the physician in charge of the therapeutic program.*
2. *The Social Service Worker discusses the patient's illness with the family, checking particularly on the following subjects:*
   (a) Accuracy of details of the patient's history.
   (b) What the patient's illness had done to the home.
   (c) What adjustments will be needed at home while he is in the hospital.
   (d) What changes must be made in the home before he can return.
3. *Clinical Psychological Evaluation*

   The test battery consists of the Wechsler Memory Scale, Bender Gestalt, H. T. P., and Kendall Graham, occasionally supplemented with the Rorschach.

   The patient is tested before and after treatment, to estimate the degree of organic impairment.

   Note:—In the past we have selected patients primarily on the basis of their history, behavior, and clinical evaluation, and have used the clinical psychological report

primarily as a means of obtaining an objective estimate of improvement. However, we have found much more improvement in cases where both the psychiatrist and the clinical psychologist concurred in the evaluation of organic factors. Hence, we are now using the test battery to help to select only those patients for treatment that have both clinical symptoms and clinical psychological evidence of organic brain disease.

4. *E.E.G., E.K.G., and photographs are obtained before and after treatment.*
5. *Initial Orientation and Transfer*

   During the time clearance is being obtained, the patient is usually transferred to the treatment ward. This is a small 10-bed open ward, with only one entrance, so arranged that one person can easily give close supervision to all patients. It has been variously called "The Old Men's Ward," "The Old Men's Club," "The Dilatation Club." All such terms were used in a friendly, joking manner, often initially by the patients themselves. The patient develops a definite group identification and is informed by the physician that he will be expected to take part in all of the program, unless specifically excused by the ward physician.
6. *Pretreatment Summary*

   Before treatment is actually started, all the data are reviewed by the ward physician with a senior staff psychiatrist, the social worker, and the clinical psychologist. Goals are established, complications anticipated, and special attention directed to any phase of the program which might impair success.

THERAPEUTIC ELEMENT 1
Daily Intravenous Administration of Histamine-Nicotinic Acid (Dilatation Therapy)

On June 5, 1950, we set aside a small 10-bed ward for further study and research on this particular therapeutic program. It is this study that is the source of the following procedures and results.

Procedure

Our procedure was designed to achieve a prolonged period of peripheral and cerebral vasodilation at as near a physiological level as possible. A profound flush, a feeling of well-being and an increased peripheral blood flow were all considered desirable. Unpleasant symptoms of headache, bounding precordium, feeling of pressure in the chest, or a drop in blood pressure approaching shock levels were considered undesirable.

Treatment was given six days a week at 8:30 A.M.

Histamine was given one day, nicotinic acid the next. (Originally we gave histamine in the morning and nicotinic acid in the afternoon. This kept the patients in bed 4-7 hours during that part of the day when the most active medical rehabilitation program was available. We seemed to be encouraging the patients to be bedfast. Consequently we arranged group activities both for late morning and afternoon and alternated the treatment each day.)

All patients were treated simultaneously in a ward which has been called by the patients "The Glow Room." Soft music on records or radio was played. Joking and banter between patients was encouraged.

Dosage

Histamine diphosphate, 2.7 mgs. (this is not histamine base, but the equivalent of 1 mg. of histamine base) in 1,000 cc. of normal saline or 5 percent glucose was given intravenously every other day.

Nicotinic acid (not nicotinamide), 200 mg. in 1,000 cc. of saline or glucose on alternate days.

The use of glucose or saline usually depended on other needs of the patient. Glucose in saline can also be used.

Rate of Flow

The rate of flow was constantly watched to achieve the therapeutic goal of dilatation without headaches or other untoward reactions. Blood pressure and pulse were recorded at 30 minute intervals as long as they stayed above 90/60. Lower pressures were watched continuously, and the rate of administration slowed 2.75 mg. usually take 60-90 minutes. This is a rate of about 0.025 to 0.075 mg./minute. The minimal effective dose is said to be 0.003, and the minimal toxic dose 0.150 mg./minute.[18]

Duration of Treatment

To a point where the patient does not need the medication or to 30 treatments—15 of each.

Description of Actual Treatment

At the beginning of treatment, the patient has an initial feeling of skin warmth. A bright red flush, particularly over the head and neck is usually seen after only a few cc's. Usually a gradual tolerance results, and after 30-40 minutes the rate must be increased to get the same results. Frequently the patients themselves will note the fading of the feeling of warmth and comfort and the loss of the flush and ask the nurse to speed it up: "Aw, come on, nurse, gimme some more, I can take it."

Treatment can be terminated at any time by cutting off the flow. Severe vascular collapse can be compensated for immediately with the use of adrenalin, which is always available.

Complications

Minor

1. Mild headaches.
2. Transient peripheral arteriolar paralysis, "boiled lobster" appearance.
3. Patchy peripheral cyanosis.
4. Bounding precordium.

Major

1. Severe headache.
2. Epigastric or precordial pain.
3. Vascular collapse—"histamine shock."
4. Increased depression.

Counterindications

Complete

1. Active Tbc.
2. Active peptic ulcer.
3. Auricular fibrillation.
4. Evidence of cerebral hemorrhage or intracranial tumor.

Partial

1. Healed Tbc lesions.
2. Healed peptic ulcer—(Anti-acid is given before treatment).
3. Hypotension—90/60 — (¼ cc. — 1/1000 adrenalin is given with histamine).
4. Cardiac or renal insufficiency.
5. Bronchial asthma—(subcutaneous skin test with histamine prior to treatment).

THERAPEUTIC ELEMENT 2
Group Occupational and Recreational Therapy

All patients who are to receive histamine-nicotinic acid dilatation therapy are treated on a special research ward; and all patients are transferred to this ward as soon as they show an adequate behavior adjustment for an open ward.

Efforts have been made to give special training and instruction to the nurses and attendants on this ward so that they may assist and encourage the patient by prompt decisions and efficient and cheerful maintenance of "the therapeutic attitude." This same attitude of helping the others is carried over to the patient; and well-oriented patients have often asked to take under their wings some more poorly oriented member of the group. All patients are expected to participate in the special program arranged for this group, which is summarized as follows:

6:30 Group is awakened.
7:00 Group goes to dining-room for breakfast.
8:00 Group returns to ward and gets in bed.
8:30 Group is given intravenous Histamine or Nicotinic Acid.
10:30 On completion of treatment—group therapy.
11:30 Group goes to dining-room for lunch.
1:00 Supervised group relaxation therapy on ward (corrective therapist).
2:00 Group attends occupational therapy sessions.
3:00 Special Service games for the group at the gymnasium.
4:00 Group goes to dining-room together.
7:00 Special parties are arranged for any movie or stage show at the recreation hall. Participation is optional.

Participation in the group is required at all times but the actual degree of participation is kept flexible to meet individual patient's needs, abilities, and interests.

THERAPEUTIC ELEMENT 3
Individual and Group Psychotherapy

Although the actual amount of time spent in psychotherapy, either individual or group, is small it is nevertheless important, necessary, and cannot be neglected. Individual psychotherapy is almost always brief, reassuring, supportive, and practical. When these patients demand passive emotional support, it must be available immediately. If it is not given immediately, these patients frequently become preoccupied with their complaint pattern, show an increased tendency toward a morbid depression, lose their identification with the group, lose the rapport with the program and the physician, and eventually require rather intensive medical workup and psychotherapy to direct them again toward recovery rather than regressive, preoccupied, hypochondriacal depression. There are several specific times when individuals require additional attention. These periods may be grouped as follows:

1. The period of orientation, when the patient first comes to the ward.
2. The periods when the patient swings toward passive dependency. This must be met with a firm push into the total program and the individual assurance that the particular complaints are not valid excuses for continued bed care.
3. The period when the patient develops a medical symptom complaint pattern. Medical problems must be met with rapid frank investigation, without allowing the investigation to interfere with routine treatment, unless specifically indicated.

Constant reassurance is needed from the nurses, attendants, and physicians, that the patient's confusion is not too serious and that he can go along with the rest of the men or "boys." We try constantly to emphasize what the men *can* still do, rather than what they are unable to do. An effort is made to teach these patients to "live with their abilities, despite their disabilities." This can be done in more detail for a larger number of patients in group therapy sessions. Frank discussions with one's aging peers, under the psychiatrist's direction, assist in the development of insight and a realistic evaluation of remaining potentials.

It is also important to encourage the patient to maintain family contacts and social interests so that reorientation on discharge will not be complicated.

THERAPEUTIC ELEMENT 4
Electric Shock Treatment

Initially we did not contemplate this type of therapy as a part of our therapeutic process. It was our intention to avoid selecting cases in which the primary disorder was a mood change. However, we found that about one-third of the patients selected because of symptoms of organic brain disease either had mood disorders (depressions) as a part of their untreated symptomatology, or developed depressions during treatment.

Early in the program, patient No. 4, after a few dilation treatments became much clearer and less confused, but at the same time much more depressed. He developed nihilistic ideas, refused to eat and became actively suicidal. It was deemed necessary to interrupt his dilation therapy for a course of 12 electric shock treatments. At the end of his shock

treatments he showed minimal depression, but rather marked confusion. He was then put on a course of 30 histamine-nicotinic acid treatments during which his confusion cleared rapidly and shortly thereafter he was able to leave the hospital.

In this group of patients, electric shock treament was used only for depressive elements. From 5-15 treatments were given, usually at the rate of two per week. Treatment was usually terminated two treatments after the patient had reached a mood and behavior level within a normal range.

Relief from confusion and improvement in memory seemed to produce an increased awareness of illness and an increased awareness of loss of personality assets. In approximately one-third of our cases this was accompanied by a marked increase in depression. Histamine-nicotinic acid therapy seemed to decrease confusion but increase depression. Similarly, electric shock seemed to decrease depression but increase confusion. We, therefore, concluded that both therapies are a necessary and integral part of the treatment program.

THERAPEUTIC ELEMENT 5
Case Work With The Family

From the time a patient is referred for evaluation for dilation therapy, the social worker begins to work with the family.

As mentioned earlier, their first assistance may be primarily diagnostic in obtaining verification of the patient's story, with particular emphasis on the time of onset of symptoms and the actual time involved in personality changes.

A major effort, which usually requires even more psychotherapeutic hours than the patients do, is readjustment of the family to the aging process. We have made numerous mistakes, such as failing to get the frank co-operation of relatives, omitting contact with all the relatives, and assuming that a patient is too disturbed to return to a particular home environment. We often have had to reverse ourselves. But from this experience we can outline the following suggestions:

1. A real effort must be made to contact every relative. Frequently distant or seldom-heard-from relatives have homes or situations where the patient is welcome.
2. Contact all of the relatives in the home. Too often one relative will give biased information and refuse to help, whereas another member will assist and plan for the continued care and supervision of the patient.
3. We have found ourselves preparing to continue hospitalization of some patients we thought were not doing well or could not make an adjustment at home, only to find that with continued treatment they improved remarkably, or the relatives were quite willing to take the patient home. One should avoid making premature decisions. Our aim now is to "let the patient write his own ticket."

The major effort is always made first with the family; but there are cases where there is no family, or where family or home are incapable of assisting. In these cases we have found it valuable to review every previous affiliation the patient had prior to hospitalization; i.e., lodge, church, business, veterans organizations, to see if there is some suitable boarding

Table 1

Summary of Thirty Patients Treated with Histamine-Nicotinic Acid
Showing age, diagnosis, number of treatments, sequence of special therapies and results.

Case Number	Age	DIAGNOSIS: Predominently Cognitive	DIAGNOSIS: Predominently Affective	DIAGNOSIS: Neurotic Inadequate	Histamine-Nicotinic Acid Therapy	Other Specific Therapies	RESULTS: Unimproved	RESULTS: IMPROVED: In Hospital	RESULTS: IMPROVED: At Home	RESULTS: IMPROVED: Markedly
1	48	X			10	15 Insulin 15 EST			X	
2	83	X			30			X		
3	60	X			26			X		
4	73		X		6 30	12 EST				X
5	54		X		30	15 EST				X
6	61	X			30	10 EST				X
7	59	X			32 60	5 EST			X	
8	53			X	30		X			
9	51		X		30					X
10	61	X			20	8 EST			X	
11	57			X	31 5	10 EST	X			
12	57	X			37					X
13	58		X		30 20	10 EST				X
14	50	X			18					X
15	48		X		19					X
16	57		X		30 19	8 EST				X
17	52	X			25		X			
18	59	X			23					X
19	58	X			6		AMA—Incomplete Treatment			
20	62		X		20				X	
21	53		X		20				X	
22	54	X			26					X
23	55			X	14		X			
24	63	X			4					X
25	54	X			20				X	
26	56	X			3 28	8 EST			X	
27							Treatment not yet completed			
28	53	X			30				X	
29	56	X			32					X
30	58			X	23		X			
TOTALS		17	8	4			5	2	8	13

home, hospital or retirement center for which he is eligible and where he can live without a complete feeling of rejection, and with a real feeling of companionship and camaraderie.

FINDINGS

We have now completed treatment on some twenty-nine consecutive patients (Table 1), selected on the constellation of symptoms listed above.

The Neurotic or Immature Group

Four of these patients (Nos. 8, 11, 23, 30) demonstrated mild perplexity and slowing, and clinically it appeared that a mild organic brain disease might be a factor in their illness. In none of these cases was this substantiated by the clinical psychologist. With further observation, partly during treatment, it became obvious that each of these patients was a long-standing passive dependent individual or a mild chronic hypochondriacal neurotic. Each had more or less assumed the cloak of confusion, perplexity, and depression, in order to satisfy neurotic or dependent needs. None was in any way affected by the histamine-nicotinic acid dilation therapy, either by clinical or psychological standards. It was necessary to deal with all of them by intensive individual therapy. All have left the hospital. They are included here only to illustrate a type of case we feel *does not benefit* by this therapy.

The Patient with Inadequate Treatment

One patient (No. 19) failed to accept orientation and education for hospitalization, staying in the hospital for only a short time and leaving against medical advice after six treatments. He was not considered to have been adequately treated.

Table 2

Results of 24 Patients with Symptoms of Organic Brain Disease Treated with the Integrated Program

	Unimproved	Improved		
		Hosp.	Home	Markedly
16 primarily cognitive dysfunction	1	2	6	7
8 primarily affective dysfunction	0	0	2	6
24	1	2	8	13
	Unimproved—1	Improved—23		

The Organic Brain Symptom Group, Adequately Treated

The remaining twenty-four patients have been divided for purpose of study into two groups: those in which the predominate presenting symptoms were in the *cognitive* field—loss of memory, disorientation, confusion—and those in which the predominate presenting symptoms were in the *affective* field—emotional instability, lack of energy, slowing down, depressed mood, and feelings of unworthiness. In almost all patients there was a little of each type of dysfunction. The results of the total program from a clinical standpoint are summarized in Table 2.

These 24 patients, we believe, give an accurate evaluation of what may be expected from this integrated treatment program. From a clinical behavior point of view, one patient was unimproved, and 23 were improved.

The *unimproved patient* (No. 17) represents a specific failure of histamine-nicotinic acid therapy only. He did not respond sufficiently to dilation therapy to warrant transfer from a closed ward to the open ward group activities.

The *two patients (Nos. 2 and 3) still in the hospital* are in need of general medical rather than psychiatric care.

Patient No. 2 is now 84 years old. One of the authors recalls the day during treatment when the patient stood by the mirror shaving himself and with a gleam in his eye stated: "This is the first time in two years that I have been able to try this, but I believe I can do it." When later teased about a few places where he had scratched himself, he replied, "Yes, I nicked myself a little, but not any worse than that barber usually does."

The other patient (No. 3) is a severe hypertensive with no family, who is now making a quiet co-operative adjustment on an open ward, going to the dining-room and undergoing occupational therapy, whereas he had formerly been in a closed ward, untidy, disoriented, and acutely disturbed by hallucinations. Although still in the hospital, he is markedly improved both from the clinical and the psychological evaluation.

The "Improved Home" group is made up of those patients who have been adequately relieved of their psychosis to the point where they are able to make an adjustment at home. From a clinical psychological point of view, they show improvement in either affective or cognitive function.

The "Markedly Improved Home" group is well enough from a clinical point of view to adjust at home and shows either very marked improvement in affective or cognitive function, or improvement in both functions. Several of these patients are again employed.

From a clinical psychological standpoint, a special effort was made to evaluate these patients, particularly immediately before and after histamine-nicotinic acid therapy. The actual number of cases studied completely before and immediately after a course of therapy was not sufficiently large to evaluate statistically, but the actual psychological tests of two patients (Nos. 18 and 22), before and after, are shown to illustrate the nature of the improvement (Plates 1 and 2). E.E.G. changes, photographs, clinical psychology results, and weight changes will be discussed in another paper.

Nine of the 24 patients received electric shock for depression. In two patients (No. 5 and No. 6) shock was given first, and in the other seven patients, after dilation therapy. In two patients (No. 4 and No. 26) dilation therapy was interrupted for shock treatment and resumed after shock treatment. Dilation therapy was given specifically for confusion and other cognitive dysfunction to the five other patients after shock treatment.

There was no appreciable statistical difference in results between those patients receiving shock and those not receiving it.

DISCUSSION

1. The Effect of Histamine-Nicotinic Acid Therapy

(a) We believe that intravenous histamine-nicotinic acid dilation therapy actually improves the function of physiologically impaired or nonfunctioning brain cells. Whether this is the result of increased cardiac output, increased vasodilatation of cerebral vessels,

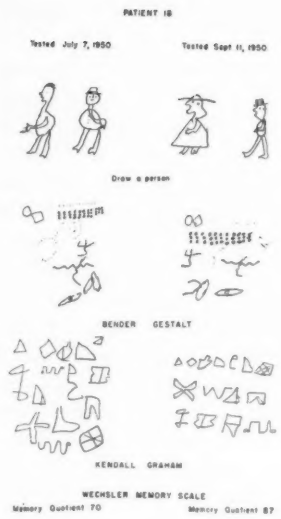
PATIENT 18
Tested July 7, 1950
Tested Sept 11, 1950
Draw a person
BENDER GESTALT
KENDALL GRAHAM
WECHSLER MEMORY SCALE
Memory Quotient 70
Memory Quotient 87
Patient received 23 Histamine Nicotinic Acid treatments from July 7, 1950 to Sept 13, 1950

PLATE 1

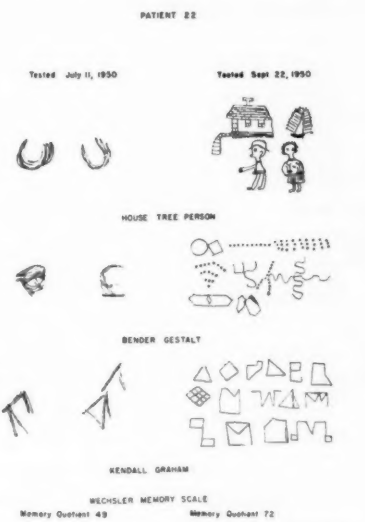
PATIENT 22
Tested July 11, 1950
Tested Sept 22, 1950
HOUSE TREE PERSON
BENDER GESTALT
KENDALL GRAHAM
WECHSLER MEMORY SCALE
Memory Quotient 49
Memory Quotient 72
Patient received 26 Histamine Nicotinic Acid treatments from July 29, 1950 to Sept 5, 1950

PLATE 2

increased capillary permeability, or an actual physiological action on the cells, we do not know. But we have seen incontinent patients who were picking and tearing at their bedclothes and loudly conversing with their hallucinations at 8 A.M. become neat, co-

Table 3

Comparison of Results Obtained With and Without Electroshock Treatment

	Total	Unimproved	Improved		
			Hosp.	Home	Markedly
Patients with predominate *Cognitive* Dysfunction					
With Shock	5	0	0	4	1
Without Shock	11	1	2	3	5
Patients with predominate *Affective* Dysfunction					
With Shock	4	0	0	1	3
Without Shock	4	0	0	1	3
All Cases					
With Shock	9	0	0	5	4
Without Shock	15	1	2	4	8

operative, and well in touch with reality by 10 A.M. after a histamine injection (Case No. 3).

We feel that the diminution in confusion and the feeling of well-being which many patients get with histamine are sufficient to give them a little more energy and put them in better touch with reality so that they can be reached better by other psychotherapeutic methods.

We believe that our patients' reactions to this treatment are so definite that the whole concept of "organic brain disease" should perhaps be re-evaluated, with consideration given to the validity of concept of "organic brain dysfunction." It is further our opinion that continued remission of symptoms with these patients may require modification of the concepts of prognosis.

(b) Histamine-nicotinic acid therapy seems to produce a very rapid remission of the symptoms of so-called "shock confusion." In addition to the "organic brain disease" patients reported here, we have also treated with histamine-nicotinic acid a group of schizophrenic patients who had reached an improvement plateau after electric shock and insulin subshock. In both groups of patients, the post-electric-shock confusion seemed to clear very rapidly. It is our impression that where post-E.S.T. confusion exists, it can be rapidly relieved by histamine-nicotinic acid therapy.

(c) Histamine-nicotinic acid therapy may be of value in other degenerative neurological diseases. Most of our patients quite clearly showed a combination of psychosis with arteriosclerosis and senile changes. A few had definite evidence of hypertensive encephalopathy.

One patient (No. 22) had been considered to have Alzheimer's disease, both from the clinical picture and from air encephalograms and electroencephalograms. His response to this therapy was a dramatic remission of most of his symptoms. Certainly a trial of this therapy is merited in similar cases.

(d) We found that histamine-nicotinic acid therapy had a definite diagnostic value. We have mentioned that certain patients with inadequate and neurotic patterns did not respond to therapy. We should also call attention to the diagnostic value of close observation of the patient while he is living with a group of his peers, and to the diagnostic value of removing the screen of confusion and cognitive dysfunction so that specific personality problems can be seen with greater clarity.

(e) The amount of drugs given, the rate of injection, the number of treatments and the use of histamine one day and nicotinic acid the next—all these were arrived at empirically. We have not had a sufficient number of patients to determine these factors by scientific experimentation. We believe the method merits that type of work-up—using only histamines, only nicotinic acid, or only glucose—in an institution where there are a sufficient number of patients so that controls can be maintained.

2. The Need for All Parts of the Integrated Program

The injection usually takes about two hours. The patient then has another 22 hours before his next injection. No matter how efficacious that two-hour injection may be, the other 22 hours are also important to the patient and to his recovery. No medicine

given over a two-hour period can be considered as the sole treatment program for this type of patient. The rest of the day also has therapeutic potential. Occupational and recreational therapy, group and individual psychotherapy, and planning for social reintegration from the day treatment is started are all integrated with the specific therapies of histamine-nicotinic acid and electric shock to obtain maximum benefit.

For example, patient No. 19 failed because of inadequate individual hospital orientation. Patient No. 17 failed because of ineffectiveness of histamine-nicotinic acid. Patient No. 31 (not reported here, since treatment was not yet completed) now has no confusion, but is depressed and would have been considered a failure had electric shock not been given. Patient No. 10 would have been considered a failure because of unsuccessful case-work therapy with the family, since after initial treatment and discharge he was returned to the hospital by his family. Since then we have arranged for him to live and work in a local tuberculosis sanitorium where he is getting along well.

3. The Reciprocal Relationship Between Confusion and Depression in Patients With Organic Brain Disease Symptoms is Noted.

In almost one-third of our cases there was definite increase in depression as the confusion and disorientation improved with histamine-nicotinic acid therapy. Intervention with electric shock therapy relieved the depression, but in several cases there was a return of confusion. This reciprocal relationship between depression and confusion in this group of patients with symptoms of organic brain disease seems somewhat similar to the inverse relationship between anxiety and depression in affective disorders as reported by Alexander.[1]

Because patients receiving histamine-nicotinic acid therapy may develop profound depressions, this treatment should be given only in hospitals or clinics with facilities to handle depressed patients. The immediate availability of electric shock therapy is considered desirable.

4. The Duration of Remission

Patients have now been followed for as long as ten months after completion of treatment and we can say that the treatment program has provided remissions for as long as ten months.* We have also seen patients with considerable improvement who relapsed ten days after treatment was completed. Second courses of treatment do not usually produce quite so dramatic an improvement, but many produce improvement that will be maintained for a longer period. We do not know how long these remissions will last. We have attempted to reinforce therapy with the use of oral nicotinic acid after intravenous therapy is stopped, and our impression is that it helps. Similarly, we tried intra-

*A recent evaluation of these patients, all of whom at the time had had no treatment for at least ten months — ten of them for fifteen months or more — showed the following results:

One patient, No. 17, in hospital, unchanged (also has CNS syphilis). Two patients, Nos. 2 and 3, in hospital, improved (one BP 250/130, the other 84 years old). Five patients, Nos. 7, 12, 18, 25, 26, at home, showed initial improvement but were essentially unchanged after 12 months. Three patients, Nos. 6, 28, 39, at home with continued improvement. Eight patients, Nos. 4, 5, 13, 14, 15, 21, 22, 24, at home, marked clinical improvement, or working part time. Five patients, Nos. 1, 9, 10, 16, 20, at home, markedly improved, working full time.

muscular injections of histamine in oil (Histamul) as a substitute for histamine but did not feel it was as effective.

SUMMARY

We have reported a therapeutic program which seems to relieve effectively a high proportion of patients with symptoms of psychosis with organic brain disease.

Twenty-nine cases have been reported. Of twenty-four patients with symptoms of organic brain disease who finished treatment, one was unimproved and twenty-three were improved; twenty-one were home; several were working.

This program is unique, we believe, in the use of intravenous histamine-nicotinic acid for this particular group of psychoses.

This is an integrated program which requires the balanced coordination of the skills and judgment of the neurologist, the psychiatrist, the clinical psychologist, the occupational therapist, and the psychiatric social worker to achieve the desired results.

RESUMEN

Hemos relatado un programa terapéutico que parece aliviar efectivamente una alta proporción de pacientes con síntomas de psicosis con dolencia orgánica del cerebro.

Se han informado ceintinueve casos. De veinticuatro pacientes con síntomas de dolencia orgánica del cerebro cuyo tratamiento se completó, uno no demostró mejoría y veintitrés mejoraron; veintiuno estaban en sus casas; varias habían vuelto a sus empleos.

En el uso de ácido histamino-nicotínico intravenoso para este grupo particular de psicosis, consideramos este programa como único.

Se trata de un programa integrado que requiere la coordinación equilibrada de las habilidades y juicio del neurólogo, del psiquiatra, del psicólogo clínico, del especialista en terapia de ocupación, y del trabajador social psiquiátrico, si se han de obtener los resultados deseados.

RESUME

Nous avons exposé un programme thérapeutique qui, selon les observations relevées jusqu'ici, soulage efficacement une proportion élevée des sujets présentant des symptômes de psychose accompagnant une affection cérébrale organique.

Le compte-rendu porte sur vingt-neuf cas. Sur vingt-quatre sujets présentant des symptômes d'affection cérébrale organique et qui ont suivi entièrement le traitement, un seul cas ne s'est pas amélioré, alors que les vingt-trois autres ont accusé une amélioration. Vingt-et-un de ces cas ont été traités chez eux; plusieurs n'ont pas interrompu leur travail.

Ce programme est unique, à notre sens, du fait de l'administration intraveineuse d'histamine combinée à de l'acide nicotinique pour le traitement des psychoses de ce groupe particulier.

Il s'agit d'un programme intégré qui exige la coordination équilibrée des talents et du jugement du neurologue, du psychiatre, du psychologue clinique, du spécialiste en thérapeutique par le travail, et du psychiatre sociologue, pour obtenir les résultats désirés.

ZUSAMMENFASSUNG

Es wurde berichtet über ein therapeutisches Programm, das einer hohen Proportion von Patienten mit Symptomen von Psychose mit organischen Gehirnerkrankungen Erleichterung zu verschaffen scheint. Der Bericht umschloss 29 Fälle. Von 24 Patienten mit Symptomen von organischer Gehirnerkrankung, die die Behandlung beendeten, zeigte einer keine Besserung, während 23 wohl eine Besserung bezeigten; 21 waren nach Hause entlassen worden; mehrere waren werktätig.

Das Program dürfte, unseres Erachtens, einzigartig sein in der Anwendung von intravenösem Histamin und Nikotinsäure für diese besondere Gruppe von Psychosen. Es handelt sich um ein zusammengeschlossenes Programm, das zur Erlangung der gewünschten Resultate eine vorsichtig abgewogene Zusammenarbeit zwischen Neurologen, Psychiatern, klinischen Psychologen, Werktherapeuten und psychiatrischen Fürsorgearbeitern erfordert.

DISCUSSION

Raymond R. Sackler, M.D.

ASSOCIATE DIRECTOR, CREEDMOOR INSTITUTE FOR PSYCHOBIOLOGIC STUDIES

The work of Moore, Morris, Smith and Lawson should contribute to the dissolution of the defeatism which has marred so much of the attitudes in regard to important entities among the psychoses.

From our own observations (to be reported) of the effects of such substances as histamine, sex steroids, etc., on psychosis with cerebral arteriosclerosis, we can lend support to their belief as to the beneficial clinical effects of histamine and the possibilities for other agents. But we must make a number of observations as to the need for caution, particularly in this indication. We have noted, in some instances, transitory effects in the ECG suggestive of coronary insufficiency—at the very least, of cardiac anoxia. Taylor[30] in his report on ten cerebral arteriosclerotics, referred to these changes as those of coronary occlusion. It must be stressed that Taylor's report, which was restricted to the use of histamine for cerebral arteriosclerotics, was negative. He observed no clinical improvements. Our clinical somatic findings correspond with his as to the potential danger of cardiac damage in cerebral arteriosclerotics, but our clinical psychiatric findings correspond to those of the current report. We must, in addition, emphasize that so potent a physiologic agent as histamine is not absolutely free of danger as some recent references made at the American Psychiatric Association meeting might suggest. There is, in addition to the possibility of cardiac effects, the theoretical and probably very real possibility of the development of adrenal insufficiency. Awareness of these two potential hazards can do much to minimize the possibility of irreversible side-effects. In our hands to date, histamine has been freer from side-effects or complication than ECT, than reports on insulin, metrazol and, of course, lobotomy.

As to the relationship of histamine to ECT, our work since 1945 and in reports in 1948, 1949, 1950 and those in the current year have stressed the fact that histamine is beneficial in certain psychoses *not only per se* — but that when ECT is used in histamine-refractory patients the total number of improvements attained was double that in our control ECT series.

These reports also pointed to the advantage of histamine pre-treatment and conjoint histamine-ECT in respect to clarity of thinking with greater freedom from the common and fairly extensive confusion and memory defects following ECT. That those undesirable ECT side-effects were minimized by vasodilatation was confirmed last year by Furtado who, at the International Congress of Psychiatry in Paris (1950), indicated similar benefits with nicotinic acid. The present paper gives further confirmation.

The authors' finding of depression in almost one-third of the patients is very interesting. This should not be viewed purely as an undesired side-effect. We have noted that as severely ill psychotics respond to therapy their improved contact with their environmnt and their improved judgment and insight as to their plight may cause a reactive anxiety and depression.

The question as to whether the beneficial effects of histamine and nicotinic acid are solely related to cerebral vasodilatation is more complicated. In one of our first series of schizophrenics studied (1945), an effect practically as dramatic as that referred to in the patient described early in the discussion was noted. Though we at that time ascribed beneficial effects of histamine primarily to vasodilatation and though Altschule and his coworkers recently reported interesting relationships between hallucinations and cerebral oxygen exchange, we found subsequently that this must be considered as a definite and important action, but it is still one of many mechanisms which are operative. The relative importance of the different mechanisms is very much open for investigation.

One other point must be made — nicotinic acid is not only a vasodilator, it is also a specific anti-pellagrous agent. The high incidence of pellagra in certain sections of the United States, the definite psychiatric syndromes, particularly psychoses, in *pellagra sine pellagra*, and the notorious frequency with which elderly patients are subject to vitamin deficiencies must also be considered in evaluating the therapeutic contributions of nicotinic acid in the present series before its benefits are ascribed *solely* and exclusively to vasodilatation. It is our belief and our practice to afford multiple and extensive vitamin supplementation in therapeutic regimens. However, in relation to experimental investigation, sharp diagnostic (both psychiatric and somatologic) delimitation of patients under study and the isolation of both therapeutic modalities and mechanisms are essential if we are to define clearly specific etiologic mechanisms in the different psychoses.

CLOSING DISCUSSION

Donald F. Moore, M.D.

We were interested in the comment on Taylor's report on coronary occlusion with histamine. We have not found this reference. I can only say that we have routinely done ECG's prior to treatment. We have had no complaints severe enough to do more than slow our injection and never a complaint severe enough to justify discontinuing treatment or getting follow-up ECG. It is quite possible that if this is a valid criticism, this should be added to our post-treatment evaluation.

Second, I am interested in the comments on the article by Furtado at the International Congress of Psychiatry, who reported on benefits of nicotinic acid in the treatment of electric shock confusion.

The discussant quotes, "The authors' finding of depression in almost one-third of the patients is very interesting. This should not be viewed purely as an undesired side effect." Such comment could be interpreted as implying that we thought that this was an undesired side effect. This is not so. We listed this not as an undesired side effect but as one of the complications of therapy. We think, as the discussant does, that there are very real psychodynamic reasons why this should occur and in general believe that this is associated with the retention of a certain amount of accurate insight and can almost be viewed as a desirable process if it is treated.

As to the value of our therapeutic process as a specific anti-pellagrous agent. It is certainly a very valid comment. A few of our patients, however, had been in the hospital and were being treated on the medical wards for some time prior to transfer to the psychiatric service and during that time had already received effective dosages of therapeutic vitamins for from several weeks to several months.

Finally, we feel the point is very well taken that research in treatment of this type of patient is exceedingly difficult because of the multiplicity of variables. It is for this reason that we have presented this as a pilot total program, the details of which need to be evaluated with control studies probably in large institutions such as in State Hospitals. It is our hope that such a program can be set up in the near future.

I would also like to add that during the recent meeting of the Third Mental Hospital Institute we reviewed our program very rapidly with Dr. Edward J. Stiegleitz. He brought out the possibility that in many of these patients a moderate degree of arteriosclerosis might definitely impair the nutrition of the brain even more than could be accounted for by the vessel constriction alone, if it is accompanied by mild anemia and the gradual diminution in basal metabolic rates described as normal for aging people. He also referred to some recent work, recalling the old kidney argument of arteriosclerosis versus arteriolar-sclerosis. I, myself, am almost certain that what we are talking about in this paper is arteriolar-sclerosis but believe that we should continue to use the larger generic term arteriosclerosis until such time as adequate proof is available that it is actually arteriolar-sclerosis.

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A Method for the Evaluation of Hormone Therapy in Schizophrenia

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Many claims are made in the literature for the merits of a great variety of therapeutic procedures in the treatment of patients suffering from mental disease. Often these results cannot be corroborated by other workers apparently employing the same drug in identical dosage and methods of administration, or using what appear to be similar psychotherapeutic procedures. Frequently the reason for these discrepancies lies in the failure of the workers to employ similar objective methods for the evaluation of the mode of treatment under consideration, even though superficially they have appeared to do so.

Engaged as we are in investigating the rôle of the adrenal cortex in schizophrenia, our interest naturally turned to a consideration of the steroid hormones as therapeutic agents in this disease. In order to ascertain the value of a steroid hormone (or for that matter, any drug procedure whatsoever) as a therapeutic agent, it became necessary to devise an objective method for the evaluation of the treatment employed. We would like to present here the method employed by us in the evaluation of various hormones as possible therapeutic agents in schizophrenia, because we think it is a method that can be applied in any study which purports to ascertain the value of a procedure or a chemical agent as a method of treatment in mental disease. The value of this method or any other method with the same objective is of course dependent upon previous knowledge of the natural course, or life history, of the disease in question.

METHOD: The method employed by us can be described best when broken down under the following subdivisions: (1) selection of subjects, (2) selection of controls, (3) grouping of subjects and controls, (4) procedures of observation, and (5) time of observations.

Selection of subjects: All of our subjects had been adjudged mentally ill and were committed to the Worcester State Hospital. From this group we selected male subjects in whom the diagnosis of schizophrenia was in no doubt. To this end, we established these criteria, namely: that each subject to be included in the study must show on examination at least two of the cardinal signs (disturbance in affect, disturbance in associations, disturbance in attention, and disturbance in cognition) of schizophrenia.

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Selection of Controls: In the selection of controls, the same standards were employed as in the selection of the subjects, i.e., all were male members of the hospital patient personnel and in none was the diagnosis of schizophrenia in any doubt.

Grouping of Subjects and Controls: The subjects and controls were grouped in pairs whenever possible. The criteria for the establishment of the pairs were concrete and embraced the following:

(1) Age: In each pair the age difference of subject and control was not greater than five years.

(2) Mode of Onset: In each pair the subject and control had similar onsets of illness. No patient in whom the onset of illness was acute was paired with a patient in whom the onset was gradual and insidious.

(3) Duration: In each pair the subject and control had similar durations of illness. In none of the pairs did the difference in duration of illness in subject and control exceed two years.

(4) Phenomenology: Subject and control in each pair showed on examination comparable behavioral abnormalities. This aspect of the pairing technique will be apparent as the case histories are reviewed.

In some of our studies, when the paucity of suitable patients precluded the pairing technique, the same criteria for selection of subjects and controls were employed, but subjects and controls were not studied in paired groups. All subjects and controls were housed on the same hospital ward during the period of study.

Procedures of Observation: In the method employed by us the subjects and controls were observed by trained psychiatric nurses and psychiatrists. Complete accounts of these observations were recorded. The internist administering the medication was the only person engaged in the study who knew which patients were receiving the hormone and which patients were receiving placebos. Thus, neither the nurses nor the doctors engaged in making the observations were aware which patients in the study were serving as subjects or which were serving as controls.

The nurses observed the patient's behavior during the entire course of the study, and recorded these observations in the twenty-four hour nurses' notes. The methods of observation employed by the psychiatrist were of two types. In one set of observations formal mental status examinations were performed, while in the other set the psychiatrist rated patients on the statistically validated psychiatric rating scale of Malamud and Sands.[1, 2] Since the purpose of this study was to evaluate certain hormones as therapeutic agents, in both methods of observation the psychiatrist avoided as much as possible becoming involved in the treatment situation. Toward this end, the patients under study were allowed to talk spontaneously without interruption and mental status and rating scale observations were made. In patients not spontaneously voluble in whom, in order to acquire knowledge of their psychiatric content, it was necessary for the psychiatrist to question

them, no leading questions were asked, suggestion was avoided, and the same questions were asked in standard fashion to subject and control. In this manner the position of the psychiatrist in the treatment situation was reduced to a minimum, the psychiatrist serving as a detached observer, and not as an active participant in the therapy.

The procedures of observation employed give three levels of information regarding the patients under study. Through the medium of the twenty-four hour nurses' notes a longitudinal record of the overt behavior of the patients in various hospital situations is obtained. From the mental status examination non-directive conversational material is obtained from the patients, and observations of the patient's behavior at certain periods during the study are made, while from the rating scale determinations directive information regarding the twenty-two items comprising the psychiatric rating scale is obtained. The rating scale scores thus obtained for each individual patient are indicative of the direction in which the patient's behavior is changing rather than the actual amount of that change, since the method itself is only roughly serially quantitative. As employed in this study, the object of the rating scale technique is standardization, which is obtained by directive evaluation of enumerated specific items. Fig. 1 shows the psychiatric rating scale of Malamud and Sands.

Time of Observations: The patients were observed by means of the three techniques described above for a period preceding the administration of the placebo or the hormone to be evaluated, during the administration and for a period after the administration of hormone or placebo was terminated. These periods were designated as the pre-treatment or control period, the period of treatment, and the post-treatment period. The length of time consumed by each of these periods varied, depending upon the hormone under study. The average length of each of these periods was two weeks for the control period and four weeks each for the treatment and post-treatment periods.

The nurses' observations on the patients were performed throughout the study from the beginning of the control period to the termination of the post-treatment period inclusively. These observations were continuous and gave longitudinal data on the overt behavior of the patients throughout the study.

The mental status examinations and psychiatric rating scale determinations, which are cross-sectional observations, were done at designated intervals throughout the study. The precise number of these observations varied with the particular hormone under study. On the average, two mental status examinations and two psychiatric rating scale determinations were done in the control period, with each of these techniques of observation being performed at weekly intervals until the conclusion of the study. These two observational procedures were staggered in time, so that the mental status examinations were done on a stipulated day early in each week of the pre-treatment, treatment, and post-treatment periods, while the rating scale determinations were performed on a designated day later in each week of these three periods. Thus, the cross-sectional observations, afforded by the periodic mental status examinations and psychiatric rating scale determinations, were so timed in conjunction with the nurses' longitudinal observations that both subjects and controls were under virtually constant observation during the period of study.

FIG. 1

PSYCHIATRIC RATING SCALE (AFTER MALAMUD & SANDS, 1940)

FUNCTION	6	5	4	3	2	1	BASE LINE		1	2	3	4	5	6
APPEARANCE	BIZARRE		DECORATIVE		OVER-METICULOUS		NEAT	CARELESS	SLOVENLY	UNTIDY	INCONTINENT		SMEARING	
MOTOR ACTIVITY	EXCITED		AGITATED		RESTLESS		ACTIVE	QUIET	UNDER-ACTIVE		RETARDED		STUPOROUS	
MIMETIC EXPRESSION	INCONGRUOUS		DRAMATIZING		EXAGGERATED		ANIMATED	RESTRAINED	STIFF		WAXY-FLEXIBILITY		MASK-LIKE	
RESPONSIVITY	ANACLITIC		SUGGESTIBLE		DEPENDENT		FLEXIBLE	RIGID	STUBBORN		RESISTIVE		NEGATIVISTIC	
HOSTILITY REACTIONS	DESTRUCTIVE		COMBATIVE		BELLIGERENT		AGGRESSIVE	SELF-EFFACING	SELF-DEPRECATING		SELF-MUTILATING		SUICIDAL	
SOCIALIZATION	DISRUPTIVE		MEDDLESOME		OUT-REACHING		EXTRAVERTED	INTROVERTED	SHUT-IN		ISOLATED		INACCESSIBLE	
EATING HABITS	OMNIPHAGIC		VORACIOUS		GLUTTONOUS		INDULGENT	FINICKY	ANOREXIC		REFUSING (SPOON-FED)		TUBE-FED	
SEXUAL BEHAVIOR	ASSAULTIVE		SOLICITING		OVER-ACTIVE		HETERO-SEX, ACTIVE	HETERO-SEX, UNDER ACTIVE	HOMOSEXUAL PASSIVE	HOMOSEXUAL ACTIVE (BY NECESSITY)	HOMOSEXUAL PASSIVE	HOMOSEXUAL ACTIVE (BY PREFERENCE)	HOMOSEXUAL ASSAULTIVE OPEN MASTURBATION	
SLEEP	SEVERE INSOMNIA		MODERATE INSOMNIA		RESTLESS SLEEP		LIGHT	HEAVY	SOMNOLENT		LETHARGIC		COMATOSE	
WORK	SCATTERED		DISORGANIZED		OVER-ACTIVE		EAGER	INDIFFERENT	SPORADIC - INEFFECTIVE		RESISTIVE		REFUSE	
ATTENTION	UNCONTROLLED		MARKEDLY DISTRACTIBLE		MODERATELY DISTRACTIBLE		ALERT	DETACHED	PREOCCUPIED		DISPARATIVE		COMPLETELY WITHDRAWN	
AWARENESS	CONFUSED	SCATTERED	SPLITTING		SUPERFICIAL		DIFFUSE	RESTRICTED	PERPLEXED	DEPERSONALIZATION		CLOUDY (DISORIENTED)	UNCONSCIOUS	
SPEECH	INCESSANTLY PRODUCTIVE		PUSH-OF-SPEECH		OVER-TALKATIVE		VOLUBLE	TERSE	UNDER-TALKATIVE	RETARDED		BLOCKING	MUTE	
ASSOCIATIONS	EGHOLALIA		KLANG		ABRUPT		DIRECT	INDIRECT	VAGUE - CIRCUMSTANTIAL	TANGENTIAL		IRRELEVANCIES	NEOLOGISMS	
MOOD	EXHILARATED		EUPHORIC		ENTHUSIASTIC		OPTIMISTIC	PESSIMISTIC	SOMBER		DESPONDENT		DEEPLY DEPRESSED	
AFFECT	INAPPROPRIATE		EXPLOSIVE		LABILE		DEMONSTRATIVE	RESERVED	INADEQUATE		BLAND		FLAT (RIGID)	
FEELING	PANIC	ANXIOUS	TENSE		HYPERSENSITIVE		SENSITIVE	CASUAL	PHLEGMATIC		DULL		APATHETIC	
PERCEPTION	HALLUCINATIONS		ILLUSIONS PSEUDO-HALLUCINATIONS		EXAGGERATED INTENSITY		EXTEROCEPTIVE	INTEROCEPTIVE	SELF-OBSERVATIONS	HYPOCHONDRIASIS		CONVERSIONS	SOMATIC HALLUCINATIONS	
THOUGHT PROCESSES	FRAGMENTED		ALOGICAL PARALOGICAL		ILLOGICAL		SHALLOW	CRITICAL	RATIONALIZING		OBSESSIVE HAIR-SPLITTING		OBSESSIVE DOUBT	
SUBJECTIVE REORGANIZATION	COSMIC DELUSIONS (OMNIPOTENCE)	DELUSIONS OF GRANDEUR	IDEAS OF PERSECUTION	IDEAS OF INFLUENCE	IDEAS OF REFERENCE	AUTISTIC	EXTRA-PERSONAL REFERENCE	INTRA-PERSONAL REFERENCE	IDEAS OF INFERIORITY	SELF-ACCUSATORY		SOMATIC DELUSIONS	NIHILISTIC	
MEMORY	CONFABULATION		FABRICATION		OBSESSIVE REMINISCENCES		PRECISE SCRUPULOUS	CARELESS VAGUE	OVER-GENERALIZATION		GAPS		DETERIORATED	
INSIGHT	NEGATION OF PROBLEM	PROBLEM EXOGENOUS	RECOGNITION OF PROBLEM WITHOUT CONCERN		SHIFTING OF BLAME		SELF-SATISFIED	SELF-CRITICAL	SELF-HYPER-CRITICAL	ADDITION OF NON-EXISTING PROBLEMS		DESPAIRING SELF-BLAME	ATTITUDE OF COMPLETE HELPLESSNESS	

HORMONES USED: Employing the method described in the first part of this paper, the following hormones were evaluated as thereapeutic agents in schizophrenia: adrenocorticotrophin (ACTH), adrenal cortical extract Upjohn (ACE), desoxycortesterone acetate (DCA), and progesterone. In the second part of this paper results of these studies will be reported.

ACTH-ACE STUDY

Evaluation I: Six patients suffering from schizophrenia were selected for this evaluation. The patients were grouped in pairs in accordance with the criteria described under Method. One patient in each pair served as the subject while the other served as the control.

The first pair was composed of patient M.B. and Patient L.A. M.B. was 36 years of age. The mode of onset of his illness was sudden. He had made a satisfactory adjustment working at his trade and attending school when he began to entertain ideas that he possessed certain unusual capabilities in scientific fields and that various people about him by unfair means were preventing him from obtaining just recognition. Dominated by his delusional and hallucinatory experiences, he forced his way into the home of a person whom he did not know and created a disturbance. He was taken into custody by the police, who, realizing that he was mentally ill, had him admitted to this hospital. The duration of M.B.'s illness was two years when he was placed on the study.

L.A. was 31 years of age. The mode of onset of his illness was acute. He had not been able to find regular employment for several months but was adjusted, living in the home of his parents where he helped with the work about the house. He began to experince visual and auditory hallucinations and entertain the idea that he was omnipotent. He fancied that various people were attempting to harm him and driven by his delusional and hallucinatory experiences he leaped from a porch. He was treated at a general hospital for the minor injuries he sustained as a result of his jump. Realizing that the patient was mentally ill, the physicians in attendance had him admitted to this hospital. The duration of L.A.'s illness was four years when he was placed on our study.

Both M.B. and L.A. showed on examination disturbance in affect, associations, attention, and cognition, and both were hallucinated, expansive, and paranoid.

After a control period of two weeks, during which the three procedures of observation, described under Method, were employed in the study of the patients, the treatment period began. Subject M.B. received ACTH* 100 milligrams by intramuscular injection once per day for the first seventeen days of the treatment period. For the final six days of the treatment period he received daily intramuscular injections of ACTH in decreasing amounts as follows: 75 milligrams per day for two days, 50 milligrams per day the following two days, and 25 milligrams per day on the final two days of treatment. Control L.A. received daily intramuscular injections of physiological saline solution throughout the entire twenty-three day treatment period.

*We are indebted to Dr. John R. Mote of the Armour Company for the supplies of ACTH used.

During the first twelve days of the control period twenty-four hours nurses' observations and mental status examinations in the case of the subject M.B. showed no change in his overt behavior or his psychiatric status. However, three days before the onset of the treatment period the nurses' observations indicated a change in M.B. in the direction of improvement, i.e., he was less explosive in his emotional reactions, he evinced an interest in and engaged in ward activities, he became less aloof and began to fraternize with the other patients, he began to cooperate with the ward personnel, he voluntarily assisted the nurses in the work about the ward, and he slept better. A mental status examination done the day before hormone therapy was instituted confirmed the nurses' observations. His affect, which had been rigid and inappropriate, was at the time of this examination, demonstrative and paralleled his thought content. His associations were direct and understandable, while in earlier examinations they had been tangential and irrelevant. He was not hallucinated or delusional, his thought processes were logical and he showed insight into his condition. This state of improvement was maintained during the first week of the treatment period. Following this, the patient showed fluctuations in his psychiatric status as indicated in the nurses' observations and the periodic mental status evaluations until the first week of the post-treatment period, when he had returned to the mental state which existed at the start of the study.

Using the psychiatric rating scale of Malamud and Sands, the results shown in Figure 2 were obtained. As can be seen, no change occurred in the subject during the control period as evidenced by this method. A definite improvement in the subject's condition occurred during the first week of treatment period as indicated by a drop in the rating scale score from 47 to 26. Throughout the rest of the treatment period the subject's condition fluctuated, as evidenced by the increase and decrease of the rating scale scores, until during the post-treatment period, when the rating scale scores returned to similar levels that existed during the control period, indicating the subject's return to the psychiatric status existing in him before the study was begun.

Using the psychiatric rating scale technique alone, timed as these observations were on the sixth day of each week throughout the study, one would think that improvement in the subject's condition, as indicated in these observations, was due to the administration of the hormone. However, with the other two procedures of observation employed in this method, i.e., the nurses' observations maintained continually through the study, and the periodic mental status examinations timed so as to occur on the second day of each week through the study, it is clear that the change in this subject's condition occurred three days before hormone administration was begun. Thus we can conclude that the changes in the psychiatric status of the subject M.B. observed by this method of evaluation of therapy were not induced by the hormone. Figure 3 graphically illustrates the timing of the three observational procedures employed in this method.

L.A., the member of this pair serving as a control, showed no change in his psychiatric status throughout the evaluation, as evidenced by nurses' observations, mental status examination, and rating scale determinations. Figure 2 shows the relatively constant rating scale scores obtained in L.A. throughout all three periods of the study.

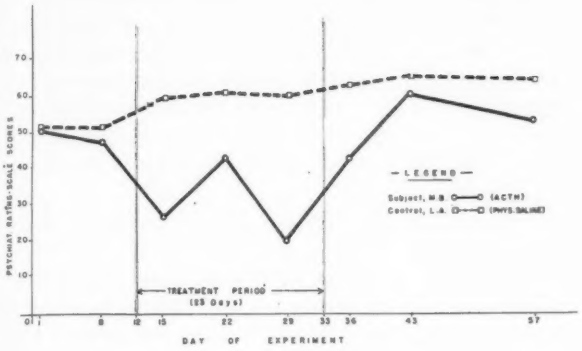

FIG. 2. Evaluation I. ACTH study:

Rating scale scores obtained in patients M.B. and L.A. throughout the observational period.

The second pair of patients employed in this evaluation was composed of subject D.W. and control B.P. D.W.was 30 years of age. The mode of onset of his illness was casual. Since childhood he had been observed to be shy, bashful, withdrawn, stubborn, irritable, and inflexible, and had exhibited bizarre behavior sporadically. At the age of 22, he was admitted to a mental hospital where he was confined for eight months. Upon his discharge from the hospital he continued to be aloof and his behavior was unpredictable, but he was able to work and maintain himself until the death of his father. After the loss of his father, D.W. became more inaccessible, irritable, and surly, culminating in an incident in which he attacked his son without provocation. Following this incident the patient was admitted to Worcester State Hospital. The duration of the attack necessitating admission to this hospital was two years when he was placed on the study.

B.P. was 32 years of age. The onset of his illness was insidious. As a child he was rigid, inflexible, and irritable. At the age of 10 he began to get into legal difficulties and was arrested on numerous occasions, culminating in his incarceration in a state prison for breaking, entering, and larceny when he was 20 years of age. Following his release from prison,

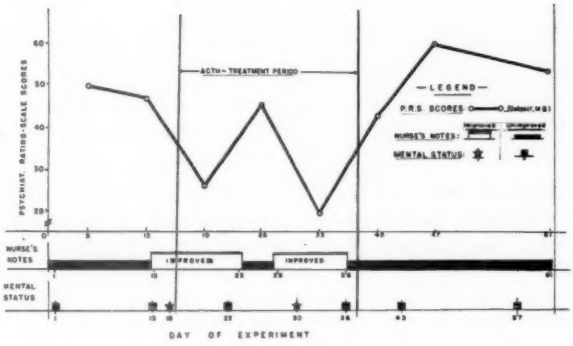

FIG. 3. Evaluation I. ACTH study:

Timing of the three observational procedures, showing pre-therapy improvement in patient M.B.

after a year's confinement, he refused to work, remained in the home of his parents where he was observed to be isolated, irritable, and sporadically belligerent. His behavior was frequently bizarre, and he talked in an incoherent manner. Since his family considered him harmless they cared for him at home and did not seek the advice of a psychiatrist. However, one day the patient attempted to steal an automobile and when apprehended insisted that the car was his own. The police took him into custody and realizing that he was mentally ill had him admitted to this hospital. The duration of B.P.'s residence in the hospital was two years when he was placed on the study.

On examination both patients showed rigidity of affect, restriction of awareness, bizarre associations, gaps in attention, illogical thinking, and lack of insight.

After a control period of two weeks, the treatment period was begun. Subject D.W. received ACE* 1cc daily by intramuscular injection for the first nine days of the treatment period. For the next thirteen days he received daily 2cc intramuscular injections of ACE. On the final two days of the treatment period D.W. received ACE 1cc and 0.5cc respectively by the same mode of administration. Control B.P. received intramuscular injections of propylene glycol throughout the same period.

Nurses' observations, mental status examinations, and psychiatric rating scale determinations revealed no changes in the status of either subject or control during the period of study. The psychiatric status of the subject remained relatively constant before, during, and after hormone administration. Figure 4 graphically illustrates the findings in subject and control during the three periods of observation.

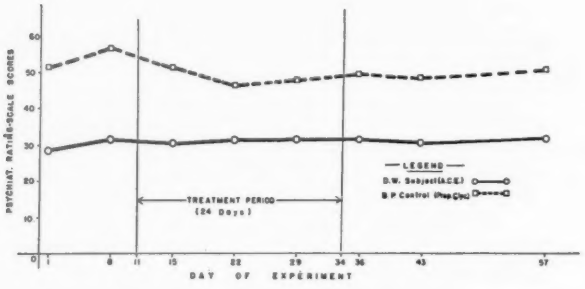

FIG. 4. Evaluation I. ACE study:

Findings on patients D.W. and B.P. during the three observational periods.

Patients D.C. and T.J. constituted the third pair selected for this evaluation. Patient D.C. was 35 years of age. The onset of his illness was insidious and its course chronic. He has had four admissions to this hospital since the age of 21. In the intervals between his periods of institutionalization his outside adjustment was borderline. The duration of his present residence in the hospital was three years when he was placed on the study.

T.J. was 33 years of age. The onset of his illness was gradual. He had a previous ad-

*Adrenal cortical extract in propylene glycol (Cortisone equivalent 40 mg. per cc) was furnished to us by the Upjohn Co. through the kindness of Dr. H. M. Kuizenga.

mission to this hospital at the age of 19, when he was confined for six months. In the interval between T.J.'s first admission to the hospital and the present admission his adjustment was not adequate, and the course of his illness slowly progressive. The duration of his present hospitalization was five years when he was placed on the study.

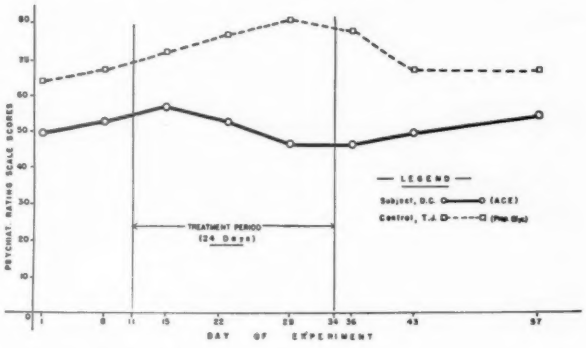

FIG. 5. Evaluation I. ACE study:

Findings on patients D.C. and T.J. during the three observational periods.

On examination both patents showed disturbances in affect, associations, and attention. In both patients, the thought processes were illogical and they were hallucinated.

At the termination of the two week control period, the treatment period was instituted. Subject D.C. received daily intramuscular injections of ACE throughout the entire treatment period, in dosages of 1cc for the first nine days, 2cc for the next thirteen days, followed by 1cc for one day, and 0.5cc on the final day of treatment. Control T.J. received daily intramuscular injections of propylene glycol during the treatment period.

No significant changes were observed in the psychiatric status of the subject before, during or after hormone administration, The control's psychiatric status became somewhat worse in the middle of the treatment period. However, it gradually changed, so that when the post-treatment was reached it had returned to the same level that existed during the pre-treatment period. Figure 5 shows graphically the findings in subject and control during the study.

Evaluation II: Four patients suffering from schizophrenia were selected for this study. Two of the patients were employed as subjects while the other two were used as controls.

After the two-week control period, subject L.M. was given 25 mg. of ACTH by intramuscular injection every six hours for twenty-five days. Subject M.B.* received ACTH 50 mg. every 6 hours for twenty-five days.

No significant changes in the psychiatric status of the subjects were observed before, during, or after hormone administration. (See Figure 6.) No significant changes were apparent in controls V.J. and E.G. employed in this evaluation. Figure 7 shows the relatively

*Although the initials are identical, subject M.B. employed in this evaluation is not the same M.B. used as a subject in Evaluation I.

constant psychiatric status maintained by each control during the three periods of observation.

Evaluation III: Three schizophrenic subjects (C.Mc., E.Y. and J.H.) were selected for this evaluation. In each one of the subjects the disease process was chronic. When this evaluation was begun C.Mc. had been a resident in the hospital for four years, while E.Y.'s and J.H.'s hospital residences were of five and four years respectively. Each one of these

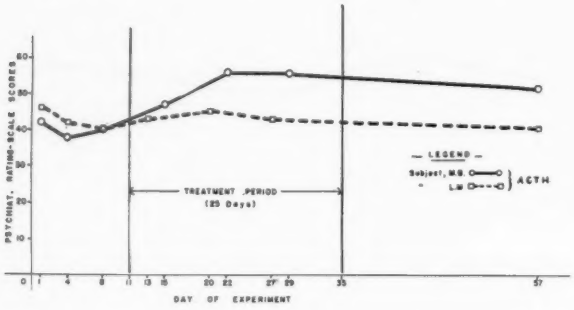

FIG. 6. Evaluation II. ACTH study:

Findings on patients L.M. and M.B. during the three observational periods.

subjects had been employed in other studies without any significant changes in their behavior having been observed, and throughout their respective hospital residences the psychiatric status of each subject had remained relatively constant.

Following the termination of the control period a twenty-seven day treatment period was instituted. During this period C.Mc. and E.Y. received 100 mg. of ACTH every twenty-four hours. The total daily 100 mg. dose was divided into three equal doses and administered by intramuscular injection every eight hours around the clock. During the twenty-seven day treatment J.H. received 1cc of ACE orally every eight hours around the clock.

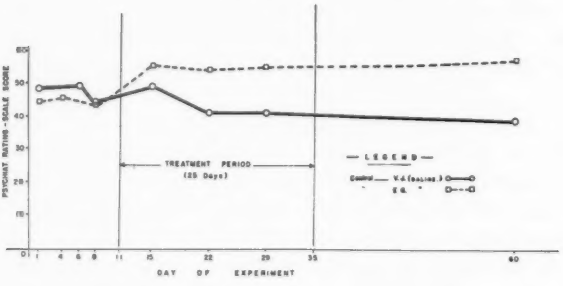

FIG. 7. Evaluation II. ACTH study:

The relatively constant psychiatric status maintained by the two controls, V.J. and E.G.

Nurses' observations, mental status examination, and psychiatric rating scale determinations revealed no significant changes in the status of the three subjects before, during, or after hormone administration. Figure 8 portrays graphically the relatively constant psychiatric status maintained by the subjects throughout the evaluation.

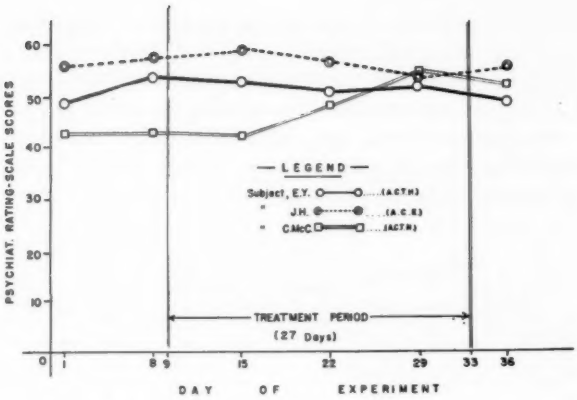

FIG. 8. Evaluation III. ACTH study:

Relatively constant psychiatric status maintained by patients C. Mc., E.Y., and J.H. during the three observational periods.

DCA STUDY

Ten patients suffering from schizophrenia were chosen for this study. Five of the patients were employed as subjects, while the remaining five patients were used as controls.

DCA* was administered to the subjects in 5 mg. intramuscular injections daily throughout the treatment period, while the controls were given intramuscular injections of olive oil.

Nurses' observations, mental status examinations, and rating scale determinations re-

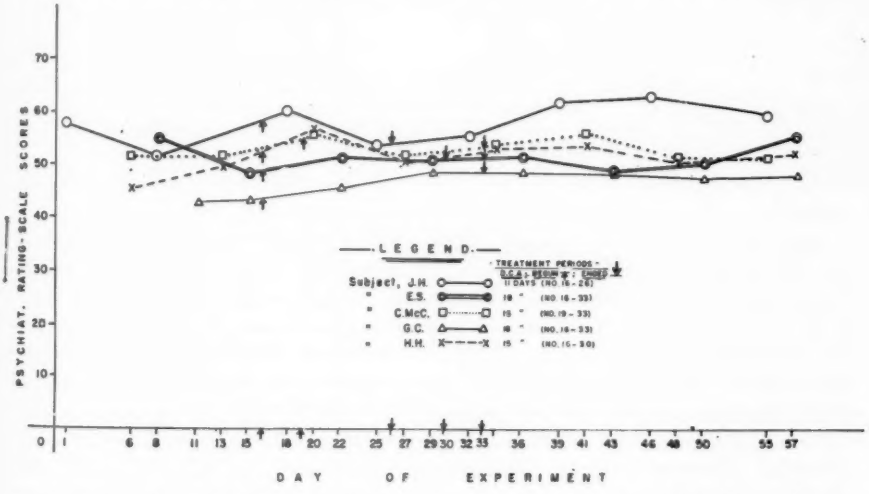

FIG. 9. DCA study: Relatively constant psychiatric status maintained by subjects throughout the observational period.

*DCA was supplied to us by the Ciba Company.

vealed no significant changes in the psychiatric status of the subjects before, during, or after hormone administration. Figure 9 shows the relatively constant psychiatric status maintained by the subjects during the study, as indicated by the lack of significant change in rating scale scores in the pre-treatment, treatment, and post-treatment periods.

No significant changes were observed in the psychiatric status of the controls during the study. See Figure 10 for a graphic portrayal of the psychiatric rating scale determination in the controls throughout the study.

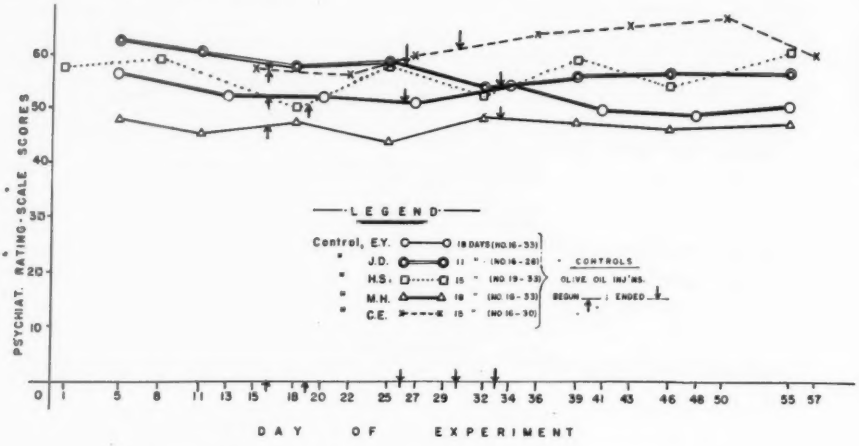

FIG. 10. DCA study: Psychiatric rating scale determinations in controls throughout the period of observation.

PROGESTERONE STUDY

For this study five male schizophrenic patients were selected. Two of these patients were employed as subjects, while the other three patients served as controls.

After a control period of seven days, during which the subjects and controls were placed on twenty-four hours nurses' observations, and one mental status examination and one psychiatric rating scale determination was performed on each patient, a thirty-one day treatment period was instituted, followed by a seven day post-treatment observational period. The same three procedures of observation, i.e., continuous nurses' observations, periodic mental status examinations, and psychiatric rating scale determinations, were employed during the treatment, and post-treatment periods as were used in the control period.

During the treatment period subject H.S. received daily intramuscular injections of microcrystalline suspension of 100 mg. of progesterone*; while subject M.A. received daily intramuscular injections of 50 mg. of the same preparation. Controls E.Y., C.E., and J.D. received daily intramuscular injections of physiological saline solution during the same period.

*Progesterone was furnished to us by the Ciba Company.

No significant changes were observed in the psychiatric status of the subjects or the controls before, or after the treatment period. Figure 11 shows the lack of significant change in the psychiatric rating scale scores obtained on subjects and controls throughout the study at the intervals indicated in the figure. Table I contains the hormone therapy schedule.

DISCUSSION: Many agents have been employed in the treatment of various psychiatric diseases, and some of these agents have been said to be efficacious in the therapy of the disease in question. Not infrequently the reports of these studies fail to supply the necessary information as to how the decision concerning the usefulness of the agent employed was reached. In other instances, though the reasons for ascribing therapeutic value to a particular agent be clearly stated, these claims are incapable of confirmation either in substance or in degree. The reasons for these discrepancies may be incident to difficulties encountered in the following spheres: (a) The choice of the disease to be investigated, (b) the selection of subjects and controls, (c) the standardization of the procedures of observations, and (d) the experimental design.

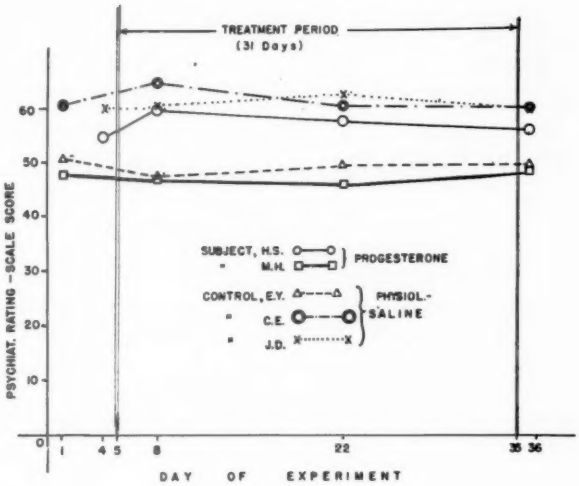

FIG. 11.
PROGESTERONE study:

Significant change in rating scale score of subjects H.S. and M.H. and controls E.C. and J.D.

It is clear at the outset that in order to evaluate an agent as a therapeutic medium in a disease process, knowledge of the natural course of that disease should be available. Following this, the patients selected to serve as subjects and controls must be those in whom the existence of the disease process under study is not in question. An important consideration in proceeding with the evaluation is to study comparable subjects and controls. This may be accomplished by studying paired patients, in which each pair is composed of a subject and a control in a similar age group, with a similar onset and duration of illness, and with like symptomatology. Consideration should be given to the standardization of the procedures of observation employed, as well as to the timing of these observations. The observations

TABLE I
HORMONE THERAPY SCHEDULE

SUBJECTS		MEDICATION	DOSE	PERIOD OF MEDICATION -DAYS-
			EVALUATION #1	
PAIR #1	M.B.	ACTH	100MGM. DAILY	17*
	L.A.	SALINE	5CC DAILY	23
PAIR #2	D.W.	ACE	DAYS 1-9:1CC/ " 10-22:2CC " 23:1CC " 24:.5CC	24
	B.P.	PROPYLENE GLYCOL	SAME AS ACE	24
PAIR #3	D.C.	ACE	SAME	24
	T.J.	PROPYLENE GLYCOL	SAME AS PAIR #2	24
			EVALUATION #2	
	L.M.	ACTH	25MGM. EVERY 6 HOURS	25
	M.B.	ACTH	50MGM. EVERY 6 HOURS	25
	V.J.	SALINE	1CC EVERY 6 HOURS	25
	E.G.	SALINE	2CC EVERY 6 HOURS	25
			EVALUATION #3	
	C.Mc.	ACTH	33MGM. EVERY 8 HOURS	27
	E.Y.	ACTH	333 EVERY 8 HOURS	27
	J.H.	ACE	1CC EVERY 8 HOURS	27
			DCA STUDY	
	5 PATIENTS	DCA	5MGM. DAILY	11-18
	5 PATIENTS	OLIVE OIL	1CC	11-18
			PROGESTERONE STUDY	
	H.S.	PROGESTERONE	100MGM. DAILY	31
	M.H.	PROGESTERONE	50MGM DAILY	31
	E.Y.	SALINE	1CC DAILY	31
	C.E	SALINE	1CC DAILY	31
	J.D.	SALINE	1CC DAILY	31

* DAYS 18-19:75MGM. PER DAY
" 20-21:50MGM. " "
" 22-23:25MGM. " "

/ CORTISONE EQUIVALENT: 40MG. PER CC

should be timed so that the patients are observed before, during, and after the administration of the therapeutic agent under evaluation. If adequately standardized and timed, the observational procedures supply the necessary information regarding the psychiatric status of the patients being studied, and reveal any changes in that status which may occur.

Many problems arise in the evaluation of treatment in patients suffering from mental diseases. In many instances the etiology, pathology, pathogenesis, and the course of the disease are unknown. Yet the psychiatrist is called upon to alter the course of the disease process in an effort to help the patient. In such a situation it is understandable that, from time to time, various claims are made for the merits of this or that therapeutic program, some of which prove to be incapable of substantiation. Certain it is that much research is necessary in this field, and one of the initial steps is the establishment of adequate objective methods for the evaluation of therapy in psychiatric diseases.

SUMMARY

A method for the evaluation of hormone therapy in schizophrenia is described. Employing this method the hormones adrenocorticotrophin, adrenal cortical extract, desoxycortesterone acetate and progesterone, were tested as therapeutic agents in schizophrenia. In the doses used, these substances have not been found to be of therapeutic value in the cases we have studied.

Difficulties encountered in devising and using our method have been discussed and principles employed in formulating an adequate objective procedure for the evaluation of therapy in mental diseases have been considered.

RESUMEN

Se describe un método de evalorar la terapia con hormonas en la esquizofrenia. Las hormonas adrenocorticotrofina, extracto cortical adrenal, desoxicorticosterona y progesterona fueron probadas por este método como agentes terapéuticos en la esquizofrenia. En ias dosificaciones empleadas se ha encontrado que estas substancias carecen de valor terapéutico en los casos estudiados por nosotros.

Se discuten las dificultades que aparecieron durante el desarrollo y empleo de nuestro método y se han considerado los principios que rigieron en la formulación de un procedimiento objetivo adecuado de evalorar la terapia en afecciones mentales.

ZUSAMMENFASSUNG

Es wird eine Methode zur Bewertung der Hormontherapie bei der Schizophrenie beschrieben. Unter Anwendung dieser Methode wurden die Hormone Adrenocorticotrophin, Nebennierenridenextrakt, Desoxycortesteronacetat und Progesteron als therapeutische Mittel in der Schizophrenie untersucht. Aus den untersuchten Fällen ergab sich der Befund, dass die genannten Substanzen in den zur Anwendung gebrachten Dosierungen ohne therapeutischen Wert sind. Schwierigkeiten in der Zusammenstellung und dem Gebrauch

der Methode werden besprochen, und die in der Formulierung einer genügend objektiven Prozedur zur Bewertung von Therapien in Geisteskrankheiten anzuwendenden Grundlinien einer Betrachtung unterzogen.

RESUME

Cet article donne un exposé d'une méthode d'évaluation de la thérapeutique à base d'hormones dans les cas de schizophrénie. Au moyen de cette méthode, on a essayé la surrénocorticotrophine d'hormones, l'extrait surréno-cortical, l'acétate de désoxycortestérone et le progestérone, en tant qu'agents thérapeutiques dans le traitment de la schizophrénie. Dans les doses utilisées, ces substances ne se sont pas montrées d'une valeur thérapeutique dans les cas que nous avons étudiés.

L'article rend compte des difficultés rencontrées dans la mise au point et l'application de notre procédé, et indique les principes mis en oeuvre dans la formulation d'une technique objective satisfaisante pour l'évaluation de la thérapeutique dans les cas de maladies mentales.

DISCUSSION

Harry A. La Burt, M.D.

SENIOR DIRECTOR, CREEDMOOR STATE HOSPITAL, NEW YORK

The authors have made a worthy contribution to an important area of psychiatric investigation—the establishment of more precise criteria. As one of a series of steps in that direction it is an encouraging trend. The value of such methods will grow through more general adoption and can be further enhanced by fuller presentations of protocols so that different investigators can compare their results within similiar frames of reference. It would have been valuable to have such information as total duration of illness, number of episodes and admissions and duration of the present episode for all patients— since other investigations have demonstrated that these factors are important determinants in regard to responsitivity to therapy. As the authors indicated by implication in their summary, conclusions drawn from their experimental results must be considered as related to the dosages they used and to the patients they tested. These were all male patients. It is suggested that progesterone might have different effects, either alone or with estradiol, for example, in female patients with schizophrenic episodes occurring post-partum. Most of the patients reported were apparently suffering with processes of several years' duration—an important element influencing therapeutic outcome.

The difficulties in setting up well-controlled research studies are multiplied by the complexities of biologic phenomena and further complicated by the special problems confronting the fledgling science of psychiatry. The authors' efforts are praiseworthy. Extension of their methods to larger numbers of patients, to patients with earlier schizophrenic processes, and to other substances and procedures (such as the psychotherapies) should be most rewarding.

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Instrumentation of Ultrasound for Biologic Quantitation

PART I OF QUANTITATED IDENTIFICATION OF PSYCHOSIS BY BLOOD SAMPLE

Raymond R. Sackler, Stanley Rich, Wilfred Roth, Mortimer D. Sackler, Co Tui, Félix Marti Ibáñez and Arthur M. Sackler

CREEDMOOR INSTITUTE FOR PSYCHOBIOLOGIC STUDIES, CREEDMOOR STATE HOSPITAL, THE VAN OPHUIJSEN CENTER

Signals reflecting the absorption of ultrasonic energy in a liquid are analyzed in an electronic computer, displayed continuously on a calibrated viscosity meter and recorded autographically.

Our conviction of the participation of neuroendocrine factors in the pathogenesis of the schizophrenic process grew out of clinical observation and a series of investigations previously reported. These elucidated biologic differences between hospitalized and nonhospitalized schizophrenics and between these psychotics and psychoneurotics. Our conviction that these differences could eventually be used for differentiation of patients and analysis of the processes at work led us to seek suitable biochemical and physical tests. The present report presents a new development in our efforts to achieve biologic quantitation in psychiatric studies and indicates the practicability of ultrasound as an instrument for dichotomous quantitated differentiation (DQD) of psychotics from nonpsychotics.

Several of the authors (A.M.S., M.D.S., R.R.S., and C.T.) had reported previously a difference in clot behavior between psychotic and nonpsychotic individuals, indicating that finer measurement of this biophysical phenomenon might yield critical information. However, the crudity of quantitation of routine clotting tests and also of our syringe test led to the utilization of an ultrasonic device* invented by Stanley R. Rich and Wilfred Roth, physicists, to measure the changes in viscosity of liquids. This instrument was originally designed to utilize ultrasonics (elastic vibrations above audibility) for automatic and continuous measurement and autographic recording of viscosity† changes of liquids and semiliquids in chemical reactions including polymerization, production of synthetic rubber, blending and fractionation of petroleum products, blood extenders and the like. In brief,

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From the Third Creedmoor Conference, November 1, 1951.

*The Ultra-Viscoson is a product of the Rich-Roth Laboratories of East Hartford, Connecticut.

†Viscosity is that property of a liquid or a gas that resists flow or change of shape. If two parallel plates each 1 cm.^{2} in area are separated by a layer of liquid 1 cm. thick, the viscosity of this liquid, *by definition*, will be 1 poise if 1 dyne of force is required to pull 1 plate parallel to itself at a velocity of 1 cm. per second with respect to the other plate. Thus, viscosity is a measure of the "internal friction" of a fluid. The molecules of a liquid are in continual motion as a result of their thermal energy and this motion increases directly with the absolute temperature. In a given imaginary plane surface in a liquid, molecules will be continually crossing this surface in both directions as a

the instrument comprises an ultrasonic probe and an electronic automatic computer.* The probe is an all-metal, ultrasonic transducer which is hermetically sealed and is designed to operate continuously over the temperature range (—150° F. to 650° F.) and in pressures from vacuum to thousands of atmospheres. The design of the probe is such that samples of liquid can be measured from 4 c.c. or less to thousands of gallons in containers varying in size from test tubes to industrial processing vats. The sensing element of the probe is a thin blade of a springlike alloy steel which protrudes from a stainless steel barrel or container as shown in the photograph.

Ultrasonic waves are produced by the probe in the liquid in which it is immersed. If sufficient liquid surrounds the probe, minute layers or laminae are caused to slip back and forth over one another at an ultrasonic frequency, the laminae experiencing bidirectional or alternating motion.† The electronic computer, attached to the probe by a cable of any desired length, instantly calculates the viscosity of the liquid from the effect of the interaction of the ultrasonic waves with molecules of the liquid. The result is graphed automatically by an electronic recorder.

For accurate measurement of physical changes in blood, care must be used to standardize on a definite volume and container since the physical characteristics being measured may be altered by the quantity of the blood and physical characteristics of the container.** Once

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result of this thermal agitation. The higher the temperature of the liquid, the more molecules cross the surface per unit time.

If the liquid on one side of the imaginary boundary is caused to move with respect to the liquid on the other side, the molecules that cross the boundary from the moving liquid have a larger component of motion parallel to the surface than do those crossing from the stationary liquid. The interaction of these will tend to prevent motion of the moving liquid and to produce motion of the stationary liquid. This can be recognized as a phenomenon similar to sliding friction, although it is termed viscosity when reference is made to liquids. Since the rate of molecular exchange across the imagined plane surface increases with temperature, equilibrium would be reached more rapidly at higher temperatures. This has been experimentally supported in the finding that viscosity decreases as temperature increases.

*The instrument has been and is being used for the study of thrombo-embolic phenomena and hemorrhagic tendencies by Drs. Raymond Yesner and Alfred Hurwitz at the Newington Veterans Administration Hospital, Newington, Connecticut.

†With concentrated high-polymer solutions, the difference between this bidirectional as compared to unidirectional motion is important for reasons beyond the scope of this paper, but for our present blood investigations, it is of only minor importance.

**Glasser reports in Medical Physics, Vol. 1, p. 217, 1950, Yearbook Publishers, that blood serum and plasma are both Newtonian liquids, but whole blood is Newtonian only if the diameter of the capillary tube in the above experiment is greater than 0.4 mm. If smaller bores are employed, the viscosity characteristic of whole blood will resemble that of a thixotrope—viscosity will decrease as the pressure increases. In living capillaries, blood flow exhibits a yield point due to interaction of the blood with the capillary walls. In this type of flow, we have a pseudoplastic. The non-Newtonian nature of whole blood can be traced to the fact that it is a suspension; i.e., gross particles, e.g., red cells, white cells and platelets, are present in suspension.

the minimum critical volume essential* for measurement is exceeded, the instrument reading is given by:

$$\text{Meter reading} = \frac{\rho}{\omega o}\left(\sqrt{g^2 + \beta^2\mu^2} + g\right) \quad (1)$$

Where: ρ = density of liquid — gms/c.c.
ωo = constant of the system
g = rigidity coefficient of liquid — $\frac{\text{dynes}}{\text{cm}^2}$
μ = viscosity coefficient of liquid — poises
β = frequency employed

For the majority of liquids, including blood, the rigidity is completely negligible and $\beta = \omega o$. Therefore, we obtain $\text{Meter reading} = \rho\mu$ (2)
as the response of the instrument.

The viscosity appears continuously on a meter calibrated in centimeter grams seconds (c.g.s.) units of viscosity: centipoises (poises $\times 10^{-2}$) times density in grams per c.c. Four ranges are provided: 0-50, 0-500, 0-5000, 0-50,000 centipoises $\times$ grams/cc. In these blood studies, only the 0-50 cp. range is utilized. A permanent graph is drawn autographically by an attached recorder, in this instance, the Brown Electronik Potentiometer. The recorder chart, driven at constant speed by its synchronous chart motor, (2 inches in 4 minutes) automatically indicates time, while a curve is traced autographically by the recorder pen (with a speed of 4½ seconds, full scale).

Routine calibration is readily-made on a Newtonian oil† of known viscosity as a standard.

*Since the Ultra-Viscoson requires a minimum depth of 0.3 mm. of liquid on the probe and since the blade is only 5 cm. long, very small volumes can be handled.

†In general, liquids can be categorized as Newtonian and non-Newtonian. If a liquid is made to flow through a capillary tube by applying a pressure difference across opposite ends of the tube, curves of flow velocity versus pressure difference can be plotted. A Newtonian liquid will obey a strict linear relationship as shown by curve I, Fig. 1. All materials not exhibiting this linear behavior are, *by definition*, non-Newtonian.

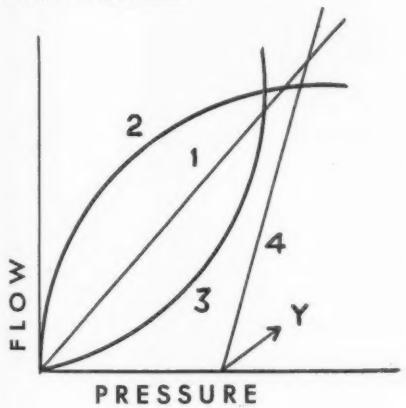

FIGURE 1

Curve 2 is that of a material having low viscosity at low pressures and high viscosity at high pressures. Starch solutions behave in this way. Such materials are called dilatants. Curve 3 is the opposite of a dilatant and represents a liquid called a thixotrope. Many colloids, suspensions, slurries, etc. are thixotropic, and, therefore, are difficult materials with which to work. Curve 4 is that of an ideal plastic. Here we must exceed a critical value of pressure, Y, termed the yield point, before any flow occurs. Once the yield point is exceeded, a true plastic behaves as a Newtonian material. There are many other possible types of non-Newtonian materials, but they exhibit characteristics similar to those already discussed.

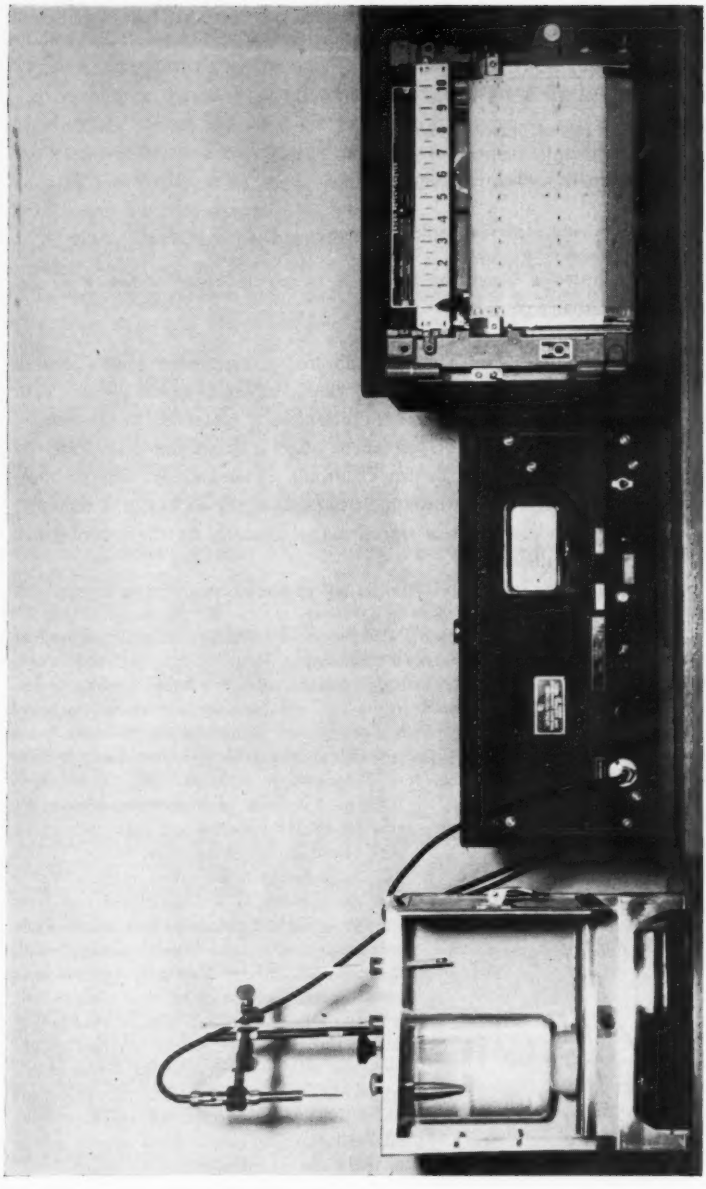

FIG. 1. From left to right. (1) Ultraviscoson probe above and centrifuge tube in constant temperature water bath. (2) Ultraviscoson unit. (3) Potentiometer.

Ultrasonic waves are propagated by the probe which is immersed in blood in the centrifuge tube. The electronic computer with the ultraviscoson unit is attached to the probe by a cable and instantly calculates the changing viscosity of the blood as it clots. The result is graphed automatically by an electronic recorder (potentiometer above).

A control in the computer is readily adjusted so that the indicating meter reads exactly the viscosity times the density of the standard. The instrument is then operating under calibrated conditions in terms of absolute fundamental quantities.

SUMMARY

Materials that change their physical characteristics with time, temperature, pressure, etc., are difficult to study unless viscosity can be measured instantaneously, continuously and automatically. Among biologic liquids, blood is most typically such a substance. Thus, quantitation of certain of its physical characteristics have long constituted a problem. The utilization of ultrasound made possible instantaneous, continuous, and automatic study of viscosity and/or other physical changes. In conjunction with standard recorders, these changes can be autographically recorded. These instruments are applicable for study of physical changes in blood and have here been utilized in an attempt to quantitate a specific physical characteristic differentiating blood of psychotic from that of nonpsychotic individuals.

ACKNOWLEDGMENTS

Any work such as this has a history—a history in terms of individuals. There are a number who, though not listed as authors, have contributed so significantly that these investigations would not have been possible without them.

Among them are three men whose convictions that the needs of mental patients can only be better served by research were so firm that they gave their support despite opposition. To these three men, Drs. Newton J. T. Bigelow, H. B. Lang, and Harry A. La Burt, our deepest appreciation for their staunch support and inspiring confidence.

For acuity of clinical observations, special reference should be made to Helen Klous, R.N., who first noted that syringes used in drawing blood from psychotics did not usually "freeze" when left untouched for a period of time.

For the unfailing and unflagging trouble-shooting and very real contributions of Heinz Norden, our sincere gratitude.

For sympathetic, intelligent, and unfailing attention to the patients of Creedmoor Institute, and full cooperation in this work, our thanks go to Eileen Jacoby, R.N., and Ann Nicoll, R.N., Eleanor Alesi, R.N., Elaine Kremens and Charlotte Grossman.

For enthusiastic participation, our thanks to psychologist Karl Steinman.

For the untiring and devoted efforts of Elizabeth Short, Florence Levin, Miriam Kent, Leemarie Burrows, our warm thanks.

On this occasion we also wish to extend our welcome and appreciation to the several new members of the Institute staff who have cooperated in this project: Dr. Rosaltha Sanders, Mrs. Lily Schmidt, and Dr. Constance Martin.

And last, but not least, our heartfelt thanks to those contributors to, and "victims" of, such research —the wives, children, husbands, and families of all those actively participating.

It is also fitting to note that the first of these series of investigations leading to this work were initiated at the van Ophuijsen Center wih the participation of the late Johan H. W. van Ophuijsen, M.D., F.A.P.A., first Clinical Director of The Creedmoor Institute.

The cost of equipment, personnel and other expenses were endowed by grants made in the memory of Isaac Sackler.

It is particularly fitting that the senior author of the first paper be Dr. Raymond Sackler, since it was at his insistence that ultrasound was added to our biologic investigative techniques.

Ultrasonometry: A New Modality in Biology and Medicine

PART II OF QUANTITATED IDENTIFICATION OF PSYCHOSIS BY BLOOD SAMPLE

Mortimer D. Sackler, Raymond R. Sackler, Co Tui, Félix Marti Ibáñez, Arthur M. Sackler, with the biometric assistance of M. B. Mittleman

CREEDMOOR INSTITUTE FOR PSYCHOBIOLOGIC STUDIES, CREEDMOOR STATE HOSPITAL, THE VAN OPHUIJSEN CENTER

A. Characteristics of The Hematosonograph (HSG).

Research leading to hematosonography is reviewed. Nomenclature is proposed and a composite hematosonograph (HSG) is presented. Certain specific quantitatable characteristics are elucidated.

B. Comparison of Hematosonographs (HSG) of Psychotics and Nonpsychotics

Analysis of certain quantitated factors of the hematosonograph (HSG) reveal variations characteristic respectively of psychotics and nonpsychotics. Following analysis, statistically significant factors are isolated for scoring.

C. Hematosonography of Oxalated Blood and Plasma

Hematosonographic curves of oxalated blood differ from those of non-oxalated blood. These findings, as well as preliminary studies with plasma, are discussed.

There has been need for improved instrumentation to quantitate more precisely progressive changes in biologic fluids. In this study the varying damping effects on ultrasound of a fluid whose physical characteristics are changing is utilized for purposes of quantitation. The use of ultrasound for measurement of certain physical properties is termed ultrasonometry (USM). The application of ultrasonometry to the biologic fluid blood, together with the autographic recording of the measurement, is herewith designated hematosonography or hemosonography (HSG). The tracing or curve from which the measurements are taken is termed the hematosonograph or hemosonograph (HSG curve).

This section records the background of the investigations which led to hematosonography. It outlines our current hematosonographic procedures and presents nomenclature for identification of the nodal points of the curve and its characteristic segments, particularly those with quantitatable attributes referable to the present investigation.

From the Third Creedmoor Conference, November 1, 1951.

BACKGROUND

In 1948, skin testing with histamine was investigated in psychotic and nonpsychotic individuals by three of the present workers (A.M.S., M.D.S. and R.R.S.) and the late Dr. van Ophuijsen. Although promising, difficulties were encountered in quantitating the resultant observed skin flare and wheal. In 1949, four of the present workers (A.M.S., M.D.S., R.R.S. and C.T.) and Dr. van Ophuijsen again attempted to differentiate psychotic from nonpsychotic by the utilization of a phytoassay procedure in which rose buds were placed in urine and observed over a period of days. This study was also complicated by problems of quantitation.

Beginning in 1950, attempts were made by the authors to quantitate the observation that syringes, into which had been drawn blood from psychotics and which were then kept for twenty-four hours with the plunger fully inserted, did not "freeze" or "jam" as consistently or as frequently as those with blood drawn from nonpsychotic individuals.

The "syringe test" was applied to over 194 psychotics and over 78 controls. Although the results were suggestive of a difference, a number of variables were present which were difficult to control, e.g., the grinding of the syringes and the force used to remove the barrel. However, some preliminary work with the "syringe test" was reported earlier this year at the Downstate (N. Y.) Interhospital Conference[1] and at the First Anniversary Dinner of The Creedmoor Institute[2]. The original observation of a possible abnormality in the blood of psychotics found support in Dr. H. B. Lang's experience with Naval personnel[3]. He had noted that oozing from venipuncture site some time after aspiration empirically suggested that the individual be carefully studied for "immaturity."

REVIEW OF HEMATOLOGIC AND RELATED STUDIES

Many hematological parameters have been subjected to scrutiny at one time or another in an attempt to elucidate a difference in the blood of psychotics. Meduna et al[4], Katzenelbogen[5], Freeman et al[6,7,8], Hoskins[9], Kety et al[10], and others[11-20] have studied not only the levels of blood constituents but also their response to varied physiological stimuli. The evidence seemed to indicate that the only consistency was inconsistency or variability of the parameters in schizophrenic patients. In 1941, Gildea[21] stated that examination of the body fluids of psychotics and nonpsychotics revealed no significant difference. However, the use of physiological stimuli as in the glucose tolerance test has since indicated that at least a difference in response is often shown by the psychotic. Abnormal glucose tolerance in schizophrenics has been reported and has been shown by other workers and ourselves to improve as the clinical status of the patient improves.

The blood eosinophile level and its response to ACTH and other physiological stimuli have been studied in psychiatric disorders by Finn Rud[22], Altschule, Parkhurst and Tillotson[23], Pincus and Hoagland[24], Cleghorn and Graham[25], Lehmann et al[26], and our own group[27-29]. Though definitive conclusions have not been reached, we have frequently

noted that some schizophrenic patients not only fail to show an eosinopenia in response to the stimulus, but also, in some circumstances, evidence an eosinophilia.

Blood enzymes have been studied by Ashby[30], Jones and Tod[31], Richter and Lee[32], and Early, Hemphill and Reiss[33], but no conclusive findings have been reported. Macht[34, 35], has investigated and reported on the effect of blood sera from psychotic patients on seedling growth. He has found that sera from psychotic patients of all diagnostic categories exert a toxic effect on seedlings.

PROCEDURE IN HEMATOSONOGRAPHY

In these two series, blood was drawn by venipuncture with an autoclaved, dry, sterile 19 or 20 gauge needle and a 20 or 10 c.c. syringe. As soon as blood entered the syringe, the Brown-Honeywell Potentiometer was started, thus recording the beginning of the test run. (Point A on HSG curve). The blood was drawn as rapidly as possible and was transferred immediately and directly to a chemically clean, dry 15 c.c. conical centrifuge tube in which the ultrasound probe was set. The tube was suspended in a constant temperature water bath at 37° C. (±1°). Care was taken so that the entire probe and the lower part of the transducer were immersed in the blood specimen and that the probe did not touch the tube. Approximately 12 c.c. of blood was required.

After the first series was completed, a change in technique was made to enable utilization of only 9 c.c. of blood by lowering the probe into the tube. This modification resulted immediately in distinct differences in the curves. Critical values were not directly comparable with the tracings taken in the original series. As a result, the data were first studied as two separate series, each with patient and control groups. Upon analysis, it is seen that this constitutes a check of the accuracy of the procedure as against itself, insofar as the changes in technique produced two entirely discrete sets of data for both patients and controls.

These, and other observations, indicate the need for continual and accurate standardization of equipment, precautions against variations in current and in the electrical circuits, changes in the characteristics of the electronic tubes, changes in the probe, differences in procedure and perhaps even including size of syringe and gauge of needles. Standardization of technique is imperative for we have reason to believe that seemingly minor alterations may also change some of the parameters being quantitated.

CLINICAL MATERIAL

A total of 73 hematosonographs (in two series, each with controls) have been analyzed —46 hospitalized and nonhospitalized patients and 27 nonpsychotic controls.

34 hospitalized patients: Of these, some were selected at random from a few of the wards in pavilions N, P, S and Reception of Creedmoor State Hospital, while others were selected at random from groups under special study by the research team. No particular criteria were used in selection beyond the presence of clinically demonstrable psychosis.

Since the selection was made from specific wards in certain pavilions, the sampling is not typical of the total state hospital population.

12 *nonhospitalized psychotics:* In order to minimize the possible contribution of nutritional differences, a group of patients of the out-patient department of The Creedmoor Institute were tested. They were chosen at random from among out-patients who had previously been "worked-up" and classified diagnostically.

Diagnostic classification of the full patient population reveals:

	Hospitalized Psychotics	Nonhospitalized Psychotics	Total
Schizophrenic (Types)	(30)	(11)	(41)
Catatonic Type	18	—	18
Hebephrenic Type	3	—	3
Mixed Type	1	—	1
Paranoid Type	7	5	12
Simple Type	—	1	1
Unclassified	1	5	6
Manic-Depressive	(1)	(—)	(1)
Depressed Type	1	—	1
Organic Psychosis	(2)	(1)	(3)
Cerebral Arteriosclerosis	1	—	1
Epidemic Encephalitis	1	—	1
General Paresis	—	1	1
Error in Classification	(1)		(1)
Control listed as patient	1		1
			46

Among the patients were 2 adolescents and 1 mother of a schizophrenic child; 12 were under treatment or were receiving medication at the time of HSG test; 1 had received therapy up to within 4 days of HSG; 4 had had lobotomy or topectomy. Details as to age, sex, duration of hospitalization, number of previous admissions, as well as prior therapies and their results are recorded in the Summary of Data Table.

27 *nonpsychotic controls:* Apparently healthy members of The Institute and hospital staff were tested at random as "normals" for the establishment of comparative control data. These included 15 doctors and dentists, 4 nurses (3 female, 1 male), 2 psychologists, 1 attendant, 3 technicians (1 female), 2 administrative personnel. No selection of any kind was exercised beyond the fact that the individuals volunteered.

The hospitalized group of patients included 34 males and 0 females; the nonhospitalized psychotics, 8 males and 4 females; while the control group had 24 males and 4 females. The tests were run under conditions of good health, although in a few instances upper respiratory infections and menstruation were present. The tests of the controls were frequently interspersed with those of the patients, in an attempt to approximate or equate for both groups such variables as temperature, time of day, relationship to meals, and season of the year.

A. CHARACTERISTICS AND NOMENCLATURE OF THE HEMATOSONOGRAPH (HSG)

The HSG, regardless of the blood sample used, has certain characteristic profiles (Fig. 1). In general, there is a short basal segment which is followed by a sharp rise; a shallow recession of moderate duration follows next, which is in turn succeeded by the major ascending segment of the curve.

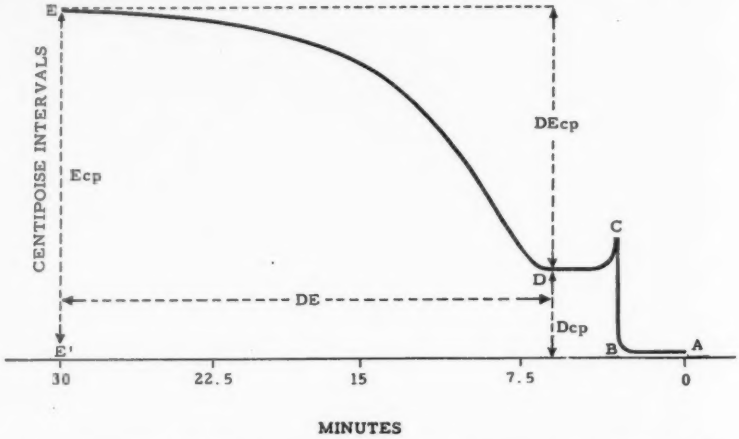

FIG. 1. Parameters and nomenclature of a stylized hematosonograph (HSG) — 30 min.

In comparing these hematosonographs, it became apparent immediately that the characteristic segments described above, and certain of their attributes, are subject to quantitative variations. In order to make the direct comparisons between two or more hematosonographs necessary to evaluate a possible dichotomy, it was found desirable to utilize a standardized system of notation for the various nodal points and segments of these curves. The nomenclature employed in this study is as follows:*

AB	The preliminary basal portion of the HSG, prior to any ascent, measured in seconds.
Ccp	The height, from the preliminary basal portion to the peak of the primary node, measured in centipoise intervals (See Part I).
D	The departure point, or takeoff point, for the major curve of the HSG.
Dcp	The height of the departure point, D, measured from the base line, in centipoise intervals.

*Other nodal points and segments of the curve have been identified but are not included in this report inasmuch as they were not utilized in scoring. These additional points of the HSG curve have been noted in blood clotting studies extending over several hours.

CD	The interval, measured in seconds, from the nodal peak, C, to the departure point, D.
CDcp	The difference, measured in centipoise intervals from the nodal peak, C, to the departure point, D.
E	The highest point attained by the HSG within 30 minutes. This is usually found at the 30 minute point, but in some instances occurs earlier (or later).
Ecp	The distance from the highest point, E, of the HSG, to the base line, measured in centipoise intervals.
DE	The interval, measured in seconds, from the departure point, D, to the highest point attained, E.
DEcp	The amount of climb from the departure point, D, to the highest point of the curve, E, measured in centipoise intervals.
DE/DEcp	The DE interval (measured in seconds) divided by DEcp (measured in centipoise intervals), resulting in an average rate of ascension of the curve, expressed as the average number of seconds required to ascend one centipoise interval.
Ecp/Ccp	The ratio of the maximum height, Ecp, to the primary nodal height, Ccp.

B. COMPARISON OF HEMATOSONOGRAPHS (HSG) OF PSYCHOTICS AND NONPSYCHOTICS

Using the technique described above, hematosonographs were made on the blood samples of the first series of 28 psychotic patients and 15 nonpsychotic controls. A second series of hematosonographs was made on the blood samples from another 18 patients and 12 more controls, but since these latter tests were run subsequent to the modifications in technique referred to above, the HSGs of this series are not directly comparable with those of Series I and are therefore evaluated separately.

After extensive study of HSG factors, the conclusion was reached that seven factors or aspects of these curves could provide a possible composite measure of differentiation; that is, that collectively these variables might constitute a dichotomous quantitative differentiation (DQD) factor to discriminate between the blood samples of the psychotic patients and the nonpsychotic controls. These seven discrete variables are discussed below, comparison being made between patients and controls prior to the change in technique (designated Series I) and those tests made on patients and controls after the change (designated Series II). (Fig. 2 and 3.)

Factor AB. Patients in Series I show an AB interval ranging from 20 to 140 seconds, while controls in this series have an AB variation of 20 to 80 seconds. Out of 28 patients, 20 (71.5 per cent) have an AB of 40 seconds or less, while 8 out of 15 controls (53.2 per cent) have an AB of 60 seconds or more. The chi-square test applied to these results shows a probability of slightly more than 10 chances in 100 that they might have arisen as a result of random sampling error or bias (chi-square = 2.56).

Series II patients have an AB range of 20-80, while Series II controls vary from 20 to

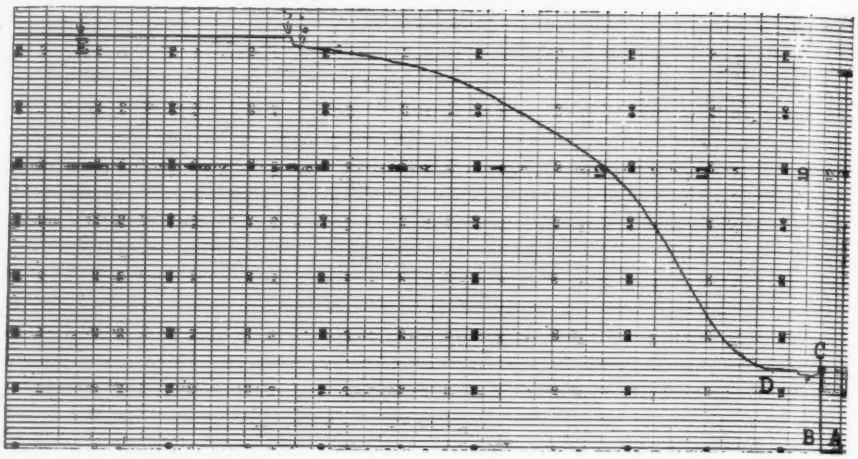

FIG. 2. Control No. CL20—Series II

	AB	Ccp	DE	Ecp	DEcp	Dcp	Ecp/Ccp	Score	Interpretation
V	40	16	1720	73	59.75	13.5	4.56		No Psychosis
S	**	22.17	0	19.46	**	20.25	19.46	81.34	

** Factor not used in Series II.

V=value as determined by measurement; S=score as determined from table of weighted scores.

70. No difference of any statistical significance was found in the AB intervals of Series II patients as compared to Series II controls.

Factor Ccp. Series I patients have a Ccp range of 17-21.5 centipoise intervals, while controls in this series range from 13 to 33.5. No statistical significance attaches to the variations of patients as compared to controls in the measurement of Ccp in Series I.

Patients in Series II show a range of 15 to 27.5, a count of 19.5 or more being characteristic of 17 out of 18 patients (94.4 per cent), while Series II controls have a Ccp range of 14 to 25, with a count of 18.5 or less occurring in 9 out of 12 controls (75 per cent). The observed difference in Ccp measurements between patients and controls in this series is highly significant statistically, a chi-square of 15.6 indicating that the chances of these differences having arisen as a result of random sampling error are considerably less than 1 in 1000.

Factor DE. The DE intervals range in Series I patients varies from 780 to 1760, and in Series I controls from 1160 to 1680. Of the patients, 22 out of 28 (78 per cent) have a DE interval of 1520 seconds or less, while in the controls 9 out of 15 (60 per cent) have a DE interval of 1560 or more. That these differences are probably statistically significant is shown by a chi-square value of 6.4, indicating slightly more than 1 chance in 100 that they might have arisen as a result of random sampling errors.

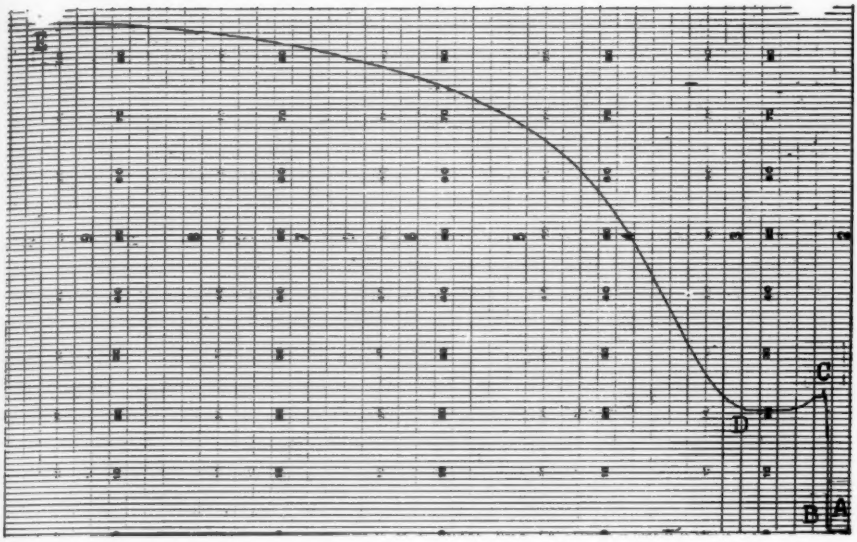

FIG 3. Patient No. 410—Series II

	AB	Ccp	DE	Ecp	DEcp	Dcp	Ecp/Ccp	Score	Interpretation
V	40	24	1580	86	65.5	20.5	3.58		Psychosis
S	**	0	0	0	**	0	0	0	Untreated

** Factor not used in Series II.

The DE interval in Series II shows an approximately similar degree of dichotomy. Patients in this series have a range of 1440 to 1720, while controls show a spread of 1200 to 1720. The DE interval is 1570 or more in 14 out of 18 patients (78 per cent), and is 1560 or less in seven out of 12 controls (58 per cent).

The chi-square value of the association between these factor values and the subject's status relative to psychosis is 4.04, indicating that the observed differences have a probability of about 4 chances in 100 of having arisen as the result of random sampling errors.

Factor Ecp. The range of Ecp in Series I patients is 40.5 to 82, with 20 out of 28 patients (71 per cent) having an Ecp measurement of 71 or less. The Ecp range in series I controls is from 63 to 81, with 11 out of 15 controls (73 per cent) having a value of 71.5 or more. The difference between patients and controls in the Ecp value are statistically significant, chi-square being 7.9, and the probability of the observed differences having arisen as a result of random sampling errors being less than 1 chance in 100.

The Ecp factor in Series II patients varies from 73.5 to 93, with 15 out of 18 patients (83 per cent) having a factor value of 76 or more. In Series II controls, the values range from 68 to 89.5, half of the controls having a measurement of 75 or less, the other half having a value of more than 76. There are approximately 5 chances in 100 that the ob-

served differences might have arisen from random sampling errors, since a chi-square value of 3.8 is obtained from these data.

Factor DEcp. This factor in Series I patients varies from 21 to 62, with 21 out of 28 patients (75 per cent) having a measurement of 52.5 or less. In Series I controls the DEcp value ranges from 44.5 to 61, with 10 out of 15 controls (66 per cent) having a value of 53.5 or more. The observed differences in these measurements are statistically significant (chi-square is 7.09), the chances being less than 1 in 100 of their having arisen as the result of random sampling errors.

The DEcp factor in Series II patients and controls shows no statistically significant difference between these groups. Patients vary from 55.5 to 71, and controls range from 48.5 to 77.5, approximately as many patients falling at each end of the range as do controls.

Factor Dcp. Series I patients have a spread of 14 to 20.5 in their Dcp scores, while controls in this group are scarcely different with a range of 15.5 to 20. No difference of any statistical significance can be determined between the scores of patients and controls in this factor.

Series II patients have a Dcp range of 12 to 26 with 15 out of 18 (83 per cent) having a measurement of 18 or more. Controls of this series range from 12 to 21, but 9 out of 12 (75 per cent) have a value of 16 or less. A chi-square value of 10.3 confirms that the chances are much less than 1 in 100 of the observed variations having arisen as a result of random sampling errors.

Factor Ecp/Ccp. This factor shows a high degree of differentiation between the controls and and patients of Series I. The patients range from 1.36 to 4.20, with 22 out of 28 (78 per cent) having a value of 3.55 or less. The controls show a range of 3.43 to 4.37, a value of 3.60 or more occurring in 12 out of 15 instances (80 per cent). Observed differences between controls and patients in this instance are highly significant statistically, chi-square = 13.77, the disparity between the results having a probability of considerably less than 1 chance in 1000 of having arisen as a result of random sampling errors.

In Series II patients the Ecp/Ccp values range from 2.75 to 5.06, with 14 out of 18 patients (77 per cent) having a value of 3.95 or less. The controls in this group vary from 3.32 to 5.32 with 9 out of 12 (75 per cent) having a score of 3.97 or more. A chi-square of 8.17, indicating a probabilty of less than 1 chance in 100 of the results having arisen as a result of random sampling errors, attests to the statistical significance of the observed differences.

C. HEMATOSONOGRAPHY OF OXALATED BLOOD AND PLASMA

The HSG curve of oxalated blood (Fig. 4) appears similar to that of plain whole blood from point A to B and C and thence to D. Thereafter, however, the HSG of oxalated blood shows change in that its DE segment differs from the arc produced by whole blood described above. The DE segment of oxalated blood or plasma is a straight line with a

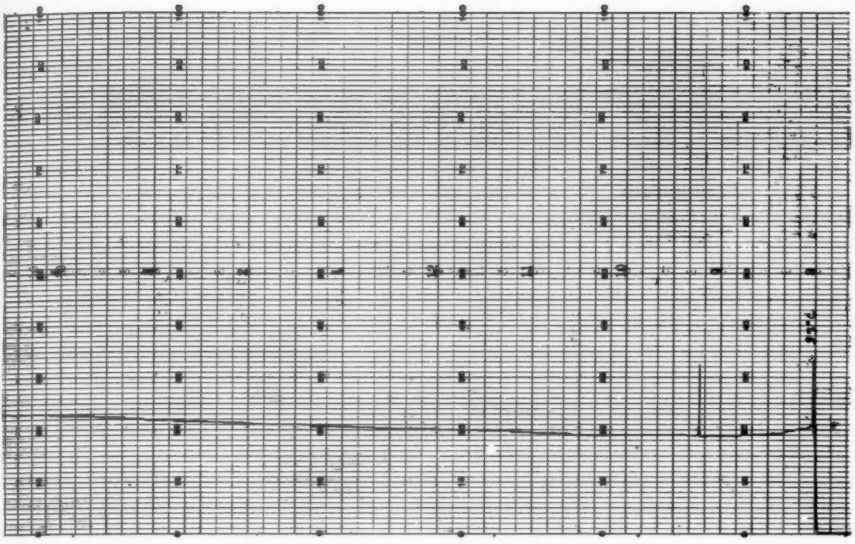

FIG. 4. Hematosonograph of Oxalated Blood.

slight upward inclination, indicating increasing viscosity and/or effects of other physical changes (possibly sedimentation).

The addition of calcium to oxalated blood is followed by such changes that the curve then approximates that of unoxalated whole blood as it clots. This suggests that the DE segment of whole blood reflects some physical change occurring in blood (presumably viscosity) associated with the process of clotting. Hematosonography thus permits for more detailed observation and measurement of the changes occurring during clotting than any method hitherto available.

HSG studies of plasma reveal a DE segment similar to that of oxalated blood; again, the addition of calcium is followed by the development of a DE arc, another indication that hematosonography is recording changes associated with clotting.

Detailed studies are currently under way with plasma and oxalated blood, as well as concurrent investigations with Lee-White clotting time, prothrombin time, blood calcium, plasma proteins, and other parameters.

CONCLUSIONS

1. The use of ultrasound for quantitating purposes is termed ultrasonometry (USM).

2. The study of blood as it clots while exposed to ultrasound used as a quantitating mechanism and the autographic recording thus made is herewith designated hematosonography or hemosonography (HSG).

3. The graphs or curves recorded in hematosonography are termed hematosonographs or hemosonographs (HSG curves).

4. Hematosonography gives a "slow-moving picture" of changes (as yet undefined, possibly in viscosity and/or other factors) in certain physical characteristics of whole blood. This picture adds the dimensions of time and viscosity (and/or other factors) to the study of blood and its components.

5. The hematosonograph is completely quantitatable both in terms of time pattern and centipoises (or centipoise intervals—the square root of the centipoise measurement). In this respect it may differ from the interpretative aspects of EKG and EEG.

6. The HSG is a curve with definitive characteristics. Nodal points have been designated for ease of reference. The parameters of the curves and certain of their mathematical functions have also been elucidated.

7. The HSG as a quantitatable record of physical changes in blood affords a new approach not to one organ as the heart or the brain, but to the most complex and ubiquitous of all systems—the blood. Since all organs and tissues contribute to the composition of the blood, its parameters must in turn reflect some aspects of their function.

8. Since hematosonography enables quantitating in terms of physical characteristics as related to time pattern, it should be explored much as spectrophotometry and chromotography have been for potential applicability, not only to metabolic studies but to basic problems in chemistry as well.

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SUMMARY OF CLINICAL DATA OF PATIENTS SERIES I

PATIENT					PREVIOUS ADMISSIONS				PRESENT ADMISSION							
						Duration	Prior		Duration to Date of HSG	Prior		Current Rx at	Elapsed Time	Total Cumulative Hospitali-		
No.	Sex	Age	Diagnosis	Pavilion	No.	in Days	Therapy	Result	in Days	Therapy	Result	Time of HSG	Since 1st Adm.	zation in Days	Remarks	HSG Score
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
619	M	42	DP.C.	S	0	0	—	0	6055	Hydro ECT ECT ECT ECT	0 0 0 0 0	HT Placebo	6055	6055	—	0
603	M	27	DP.C.	S	1	124	Ins	‡	2680	ECT HT Pro-HT	0 0 0	None	3637	2804	—	0
625	M	23	DP.C.	S	1	1005	ECT Ins-ECT	0 ‡	355	—	0	None	1365	1347	—	0
231	M	36	DP.C.	N	0	0	—	0	1425	ECT Ins T/E	0 0 0	None	1425	1425	—	19.46
623	M	24	DP.C.	S	0	0	—	0	3070	Ins	‡	HT-Placebo	3070	3070	Acne	0
620	M	44	DP.C.	S	0	0	—	0	2368	—	0	HT Pro	2368	2368	—	0
211	M	47	DP.P.	P	1	436 2073	—	0	709	Preg T/E	0 0	None None	6205	3218	—	0
226	M	22	DP.C.	S	0	0	—	–	1013	Ins ECT Pent. Int. T/E T/E-Pro	0 0 0 † ¶C.S. Ret.	None	1013	1013	—	0
633	M	27	DP.C.	S	1	336	ECT, But	‡	3833	ECT	0	None	5375	4169	—	20.00
220	M	18	DP.H.	S	1 2	28 235	ECT	–	698	T/E T/E T/E	0 0 †	None	1395	961	—	18.06
622	M	31	DP.C.	S	1	360	Ins	‡	3070	ECT	0	HT Pro	3650	3430	—	18.06

77	M	32	DP. GP.?	OPD	–	—	—	–	365	Pen HT	Therapy Incomplete	None	367	382	—	18.06
134	F	38	DP.P.	OPD	0	—	—	–	614	—	–	None	635	—	—	18.06
624	M	38	DP.C.	S	1	365+	Ins	‡	3285	ECT	0	HT	4380	3650+	—	18.06
										ECT	0	Placebo				
630	M	40	DP.P.	S	1	3	—	0	3847	ECT	0	None	4845	4556	—	18.06
75	M	61	DP.P.	OPD	1-H 3-OPD	121	ECT	‡	316	HT	‡	T/E	2555	121	—	20.00
							ECT	0		T/E						
							Psycho-therapy	0		ECT						
85	M	16	DP.P.	OPD	0	0	—	–	183	T/E	‡	HT	356	356	—	20.00
627	M	30	DP.C.	S	1	1460	NO_2 Benz									
							ECT	‡	745	ECT	0	None	2385	2205	—	20.00
168	F	33	DP.U.	H	3-H	90	ECT	†	26	—	–	None	34	90	Palp. Thyr; Trem; Tach;	20.00
							Ins	†								
165	F	33	DP.U.	OPD	1	181	P. Anal.	–	28	None	–	HT	664	88	—	20.00
							Ins	–								
							ECT	–								
140	F	39	DP.U.	H	0	0	—	–	172	None	–	HT	172	172	Ir. Men; BMR-O	21.94
138	M	32	DP.P.	H	1	150	—	–	190	None	–	HT	190	215	Fem. Contour Enl. Breasts Obesity	40.00
618	M	40	DP.C.	S	0	0	—	–	7665	ECT	0	HT Pro.	7665	7665*	1930 Palp. Thyr.	40.00
626	M	29	DP.C.	S	1	50	—	0	2920	ECT	0	None	3650	2970	—	61.94
										ECT	0	To go on HT				
										ECT	0					
										Top	0					
621	M	25	DP.C.	S	1	0	—	0	1095	ECT	0	HT	2190	1825	—	61.94
										ECT	0	Pro				
										ECT	0					
616	M	43	DP.C.	S	0	0	—	0	8030	Met	0	HT	8030	8030	—	61.94
										ECT	0	Pro.				
										ECT	0					
631	M	23	DP.M.	REC	0	20	—	–	39	None	0	None	59	59	—	80
221	M	19	DP.H.	S	0	0	—	–	1030	ECT-Ins	0	None	1030	1030	—	100
										T/E	0					
										T/E	0					
										T/E	0					

SUMMARY OF CLINICAL DATA OF PATIENTS: SERIES II

PATIENT No.	Sex	Age	Diagnosis	Pavilion	PREVIOUS ADMISSIONS No.	Duration in Days	Prior Therapy	Result	PRESENT ADMISSION Duration to Date of HSG in Days	Prior Therapy	Result	Current Rx at Time of HSG	Elapsed Time Since 1st Adm. in Days	Total Cumulative Hospitalization in Days	Remarks	HSG Score
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
403	M	60	Psy. with Cer. Art.	N	0	0	—	–	1131	ECT Preg	0 0	None	1131	1131	—	0
602	M	17	Psy. with epid. enc.	S	1 2 3	100 3425 30	— — —	– – –	534	HT T/E-HT Pro-HT-T/E	0	None	4371	4089	—	0
507	M	51	DP.P.	N	1 2 3	66 50 2359	— — —	0	2916	None	0	None	5410	5391	—	0
508	M	44	DP.H.	N	1	375	—	–	8040 (7665)	None	0	None	8040	8040	—	0
410	M	65	DP.P.	N	3-4 5	? 1640	Ant —	0	1034	ECT Preg	0 0	None	6935	1674+	—	0
634	M	30	DP.P.	P	3	363	Ins Met	– ‡	2692	ECT Top	0	None	2920	2692	Homo	0
605	M	30	DP.P.	S	1 2	197 776	Ins Fev	(‡) ‡	1232	ECT Lob ECT HT Pro	† (‡) 0 0 0	None	2413	973	—	0
229	M	34	DP.C.	N	1	7	—	–	5220	T/E	0	None	5585	5227	—	18.06
V1A	M	51	DP.P.	OPD	0	—	—	–	680	ECT HT	¶	None	—	—	—	18.66
216	M	54	MD.D.	N	1	?	?	0	773	ECT Preg T/E	0 (‡) (‡)	None	3390	773	—	0
28	M	23	DP.S.	OPD	0	—	Glu	–	505	HT Pro	§	None	505	511	Moist extreme cold Obese	19.45
629	M	29	DP.C.	S	0	0	—	–	3675	Met ECT	† 0	None	3675	3675	—	19.46
231A	M	36	DP.C?	N	0	0	—	–	1425	ECT Ins T/E	0 0 0	None	1425	1425	—	0

632	M	30	DP.P.	S	0	0	—	–	3389	ECT Top	0 0	None	3389	3389	—	19.46
635	M	25	DP. Ment. Defec.	REC	0	0	Ant-Pit Thyr ECT	†	15	None	0	None	2100	15	Hypo. Thyr. Cretin? Fro. Hypogonad.	20.25
147	M	17	DP.U.	H	0	—	—	–	177	None	0	HT	177	177	—	38.12
18	M	15	DP.U.	H	1-OPD	965	Group	Deteri- orated	544	HT-Pro T/E	§ §	Pro	1539	None	Cysts Hypogonad.	39.71
CL24**															—	61.87

EXPLANATION FOR SUMMARY OF CLINICAL DATA OF PATIENTS: SERIES I

Diagnosis (Column 4)
- DP.C.—Dementia Praecox Catatonic
- DP.H.—Dementia Praecox Hebephrenic
- DP.GP.—Dementia Praecox, General Paresis
- DP.P.—Dementia Praecox Paranoid
- DP.U.—Dementia Praecox Undetermined
- DP.S.—Dementia Praecox Simple
- DP.M.—Dementia Praecox Mixed

Therapy (Column 8, 11) Rx (Column 13)
- Ins—Insulin
- ECT—Electroconvulsive Therapy
- But—Butanol
- NO_2—Nitrogen oxide
- Benz—Benzedrine
- P.Anal.—Psychoanalysis
- Hydro.—Hydrotherapy
- HT—Histamine
- Pro—Proloid
- T/E—Testosterone with Estrogens
- Preg.—Pregnenolone
- Pent. Int.—Pentothal Intramuscular
- Pen—Penicillin

Result (Column 9)
- 0—Unimproved
- †—Slight improvement
- ‡—Some improvement
- ¶C.S.—Improved Convalescent status
- Ret.—Returned

Remarks (Column 16)
- Palp. Thyr.—Palpable Thyroid
- Trem.—Tremor, hands
- Tach.—Tachycardia
- Ir. Men.—Irregular menses
- BMR-O—Basal metabolism rate for obesity
- Fem.—Female
- Enl.—Enlarged

EXPLANATION FOR SUMMARY OF CLINICAL DATA OF PATIENTS: SERIES II

Diagnosis (Column 4)
- Psy. with Cer. Art.—Psychosis with cerebral arteriosclerosis
- DP.P.—Dementia praecox paranoid
- DP.H.—Dementia praecox hebephrenic
- DP.C.—Dementia praecox catatonic
- MD.D.—Manic depressive depressed
- DP.S.—Dementia praecox simple
- DP. Ment. Defec.—Dementia praecox (Mental Defective)
- DP.U.—Dementia praecox undetermin
- Psy. with epid. enc.—Psychosis with epidemic encephalitis
- CL24**—Control erroneously entered as patient

Therapy (Column 8) (Column 11) Rx (Column 13)
- Ant—Antuitrin
- Ins—Insulin
- Met—Metrazol
- Fev—Fever Therapy
- Glu—Glutamic Acid
- Top—Topectomy
- Thyr—Thyroid
- ECT—Electroconvulsive Therapy
- Preg—Pregnenolone
- HT—Histamine
- T/E—Testosterone with Estrogens
- Pro—Proloid
- Ant-Pit—Anterior pituitrin
- Lob—Lobotomy

Result (Column 9)
- ‡—Some improvement
- †—Slight improvement
- (‡)—Temporary improvement
- 0—No improvement
- §—Improvement
- ¶—Improvement

Remarks (Column 16)
- Homo.—Homosexual
- Hypo. Thyr.—Hypothyroid
- Hypogonad.—Hypogonadism
- Fro.—Froehlich's syndrome

Dichotomous Quantitative Differentiation (DQD) of Hematosonographs of Psychotics from Nonpsychotics

PART III OF QUANTITATED IDENTIFICATION OF PSYCHOSIS BY BLOOD SAMPLE

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Mathematical analysis of physical data from a blood sample identifies psychoses with a level of accuracy exceeding 83 per cent in 73 subjects (46 patients, mainly hospitalized and non-hospitalized schizophrenics and 27 non-psychotic controls)—with a resultant chi-square of 31.77. Further differentiation between treated and untreated psychotic patients is also attained with an accuracy in excess of 80 per cent and a chi-square of 10.57.

The relationship of metabolic factors to psychiatric processes is revealed in much of our physiologic findings[1-4] and has been discussed to some extent in our report—Physiodynamics of Major Metabolic Disorders[5, 6]. Our research flow chart, originally projected in 1948, while devoted fundamentally to psychiatric investigation, has, for several years, suggested areas of investigation not only in endocrinology but also in other metabolic deviations: in surgery, as in the treatment of burns; in obstetrics and gynecology, as in possible new tests for pregnancy; and in internal medicine, as in certain complications of diabetic ketosis. Unless one has experienced such findings, which relate clinical entities to fundamental biological processes, it can come as something of a shock that two pure physical sciences, physics and mathematics, can by themselves enable differentiation of a psychotic from a nonpsychotic simply on the basis of a blood specimen. Conversely, as can be seen, the demonstration of such a fact can afford, in a measure, significant counterproof —to borrow a word from Claude Bernard—of the great import of pathophysiologic factors, particularly neuroendocrine, in the bodily processes associated with psychoses.

OBJECTIVES

The present investigation sought:

1) to apply the quantitated critical factors obtained by hematosonography so as to determine whether a dichotomous quantitated differentiation (DQD) exists between psychotics and nonpsychotics;
2) to determine the statistical significance of such findings.

From the Third Creedmoor Conference, November 1, 1951.

RESULTS

Dichotomous Quantitative Differentiation (DQD) of Hematosonographs of Psychotics

It will be observed from comparison of the hematosonographs of psychotics and nonpsychotics, analyzed in the preceding paper, that a differential exists in the relative dichotomization of these curves when any single factor is compared with another. For example, in Series I the Ccp factor is not usable for the dichotomous quantitative differentiation of these HSG curves, whereas in Series II the Ccp factor is an extremely useful variable, correctly identifying 26 out of 30 hematosonographs as to their psychotic or nonpsychotic origin. The variation in predictive value of the several factors in one series as compared to another arises from the gross qualitative changes induced in the hematosonographs as a result of modification of technique. Thus, in order to assay the dichotomous differentiating ability of the hematosonographs for the tests run before and after change in technique, those factors which show the highest indication of prediction for each series have been selected.

In the case of Series I patients and controls, the factors used to determine the possible dichotomy of psychotic as compared to nonpsychotic were AB, DE, Ecp, DEcp, and Ecp/Ccp. Each of these factors was assigned a scoring weight according to its proportional contribution to the total obtained differentiation of the two types of hematosonographs.* Thus, the following scoring weights were employed:

Factor	*Weight*
AB	18.06
DE	20.00
Ecp	20.00
DEcp	20.00
Ecp/Ccp	21.94

*The method of weighting each factor for its contribution to the total score is predicated upon the degree of dichotomy shown by the individual factor relative to all the factors used. This method is best illustrated by a hypothetical example wherein we may designate three factors respectively as X, Y, Z. Let us assume that factor X correctly identifies 75 per cent of our subjects as to psychotic or nonpsychotic. Let us then make the further assumption that factor Y correctly identifies 80 per cent of our subjects, and that factor Z correctly identifies 85 per cent of our subjects. We then add these percentages of identification (75 per cent + 80 per cent + 85 per cent) and obtain a total of 240. The contribution which each of the factors, X, Y, Z has made to the total of 240 then becomes the scoring weight for the respective factor. Thus, factor X with a 75 per cent identification contributes 31.2 per cent of the total weight and is therefore given a scoring weight of 31.2; factor Y has a contributory value of 33.3 per cent to the total of 240 and is therefore accorded a scoring weight of 33.3; finally, factor Z is found to contribute 35.4 per cent of the total of 240 and is thus accorded a scoring weight of 35.4. Since the total of these three factors is now 99.9 and should be 100.00 (the difference of .1 arising from the rounding off of arithmetic fractions), the differential of 0.1 is added to Z, the factor with the highest identification rate, thus giving it a 35.5 scoring weight.

The process of actual dichotomization of the HSG curves of patients and controls proceeded as follows: for each factor the actual value observed on the curve was recorded, if the value fell within the observed critical range of controls, (i.e., that range which includes the majority of controls), the factor value was given a scoring weight according to the protocol above.* The weighted scores were then added, and if the total was 50 or less, the HSG was considered to be that of a psychotic patient; if the total weighted score was 51 or more, the HSG was identified for the purpose of this test as being that of a non-psychotic control.

Results of the foregoing method of testing the dichotomous differentiating ability of the hematosonographs of Series I patients and controls are seen in the following protocol:

	Score		
Series I	<50	51>	Number
Patients	23	5	28
Controls	4	11	15
	27	16	43

*The method of scoring the individual hematosonograph is predicated upon the values of the specific factors and the weighted score accorded each such factor.

In Series I the combination of the following five factors was found to produce a high degree of dichotomy between patients and controls: AB, DE, Ecp, DEcp and Ecp/Ccp. For example, upon inspection of our data we find that factor Ecp/BC correctly identifies 72 per cent of our subjects according to whether the Ecp/Ccp value is 71 or less (patients) or 71.5 or more (controls). Since as shown in our protocol, factor Ecp/Ccp in Series I carries a scoring weight of 21.94, we accord this score whenever the Ecp/Ccp value is 71.5 or more. If the Ecp/Ccp value is less than 71.5, the subject receives a score of zero for this particular factor.

Using the foregoing method, we score Series I subjects as follows:

Factor	*Critical Value*	*Score*
AB	60 or more	18.06
DE	1560 or more	20.00
Ecp	71.5 or more	20.00
DEcp	53 or more	20.00
Ecp/Ccp	3.6 or more	21.94

If the total score is 50 or less, the subject is identified as a patient, if the total score is 51 or more, the subject is identified as a control.

The same method is used for scoring Series II subjects, but with different factors and weights:

Factor	*Critical Value*	*Score*
Ccp	18.5 or less	22.17
DE	1560 or less	18.66
Ecp	75 or less	19.46
Dcp	16 or less	20.25
Ecp/Ccp	3.97 or more	19.46

As with Series I subjects, a total score of 50 or less is considered to identify a patient, while a total score of 51 or more is used to identify a control.

The above protocol indicates that 79 per cent of the subjects in Series I are identifiable as to a psychotic or nonpsychotic state on the basis of their hematosonographs. That the observed dichotomy is highly significant statistically is attested by a chi-square value of 12.86, indicating the probability of considerably less than 1 chance in 1000 that these differences arise from random sampling errors.

The same system of testing dichotomy, and method of weighing, was used for the subjects of Series II. In this instance, the factors used and their relative scoring weights were as follows:

Factor	*Weight*
BC	22.17
DE	18.66
Ecp	19.46
Dcp	20.25
Ecp/Ccp	19.46

The results of this test of dichotomy in Series II patients and controls are set forth in the following protocol:

	Score		
Series II	<50	51>	Number
Patients	17	1	18
Controls	2	10	12
	19	11	30

The dichotomous ability of the hematosonograph in differentiating between psychotic and nonpsychotic blood in the case of the Series II subjects is well shown in these data. The results have a high degree of significance, chi-square being 18.75.

A comparison of Series I patients scores with Series II patient scores shows a somewhat higher score trend in Series I patients, half of the group of 28 having a score of 20 or more, the other half having a score of less than 20; Series II patients, as a result of slightly different weights being used, largely have scores of less than 20, since 14 out of 18 scores were less than 20. However, these differences are statistically not significant and arise as a result of sample error, since a chi-square value of 3.55 is obtained in testing the association of score between Series I and II. The difference between the scores of Series I controls as compared to Series II controls is even smaller, since virtually an even split occurs in the scores of these two groups. Controls of Series I have a score of 81.34 or more in 6 out of 12 cases, while controls of Series II have a score of 78 or less in 8 out of 15 cases. A chi-square value of 0.02 confirms the fact that the observed minor difference is almost certainly (90 chances out of 100) due to sampling error and therefore statistically validates pooling of the two control samples.

The foregoing comparisons of controls and patients in both groups indicate the validity of considering patients of both groups as insignificantly differentiated from each other,

while controls may similarly be regarded as homogeneous so far as their hematosonographic scores are concerned. The question remains as to whether the pooled patient sample is significantly dichotomized from the pooled control sample. The following protocol shows the direct comparison of all patient scores with all control scores:

	Score		
	<50	51>	Number
Patients	40	6	46
Controls	6	21	27
	46	27	73

As indicated in the above protocol, 61 out of 73 subjects (83.5 per cent) for whom hematosonographs were taken and scored, can be correctly identified as psychotic or non-psychotic on the basis of their hematosonographic scores. The observed differentiation on the basis of the hematosonographic scoring is strongly significant, the results showing a chi-square value of 31.77 and consequently being a certainty for all practical purposes of an origin independent of sampling errors.

In reviewing the data on the 6 psychotic patients whose scores fall within the normal range of the controls, we find that 3 were on medication at the time of the test (histamine, thyroid and/or propylthiouracil).

Review of the data on the 6 controls, whose scores fall below the normal range, reveals the possibility that upper respiratory infection and menstruation may cause significant deviation in the HSG score, since 3 of the 6 were either menstruating and/or with a cold.

Hematosonographic Comparison of Treated and Untreated Psychotics

As one observes the sharpness of the dichotomization between patients and controls (Fig. 1), it becomes evident that:

(a) The samples used are highly representative of their respective populations; (b) there were "contaminants" which could yield findings of great significance.

In graphing untreated psychotics vs. control nonpsychotics, one finds the dichotomization still more clearly apparent. (Fig. 2).

Analysis of these two groups reveals a DQD in excess of 88 per cent with a chi-square of 36.04 indicating considerably less than 1 chance in 1000 of the observed differentiation having arisen as a result of random sampling errors.

Examination of the HSG scores of all 46 psychotic patients studied during the course of the present investigation shows an important and significant dichotomy between the scores of patients treated or receiving certain medication within four days of the time of their HSG test, and those patients who were completely untreated or who had been treated or administered certain medications more than four days prior to their HSG test. (As used here, the term "treatment" refers to administration of any of the following: Proloid, sex steroids, histamine, propylthiouracil).

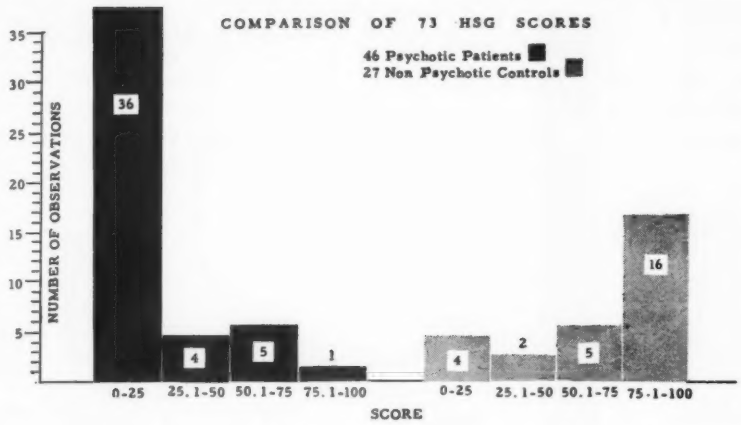

FIGURE I: Dichotomous Quantitative Differentiation of Psychotic Patients from Controls = 83.5%; $\chi^2 = 31.77$

In 34 untreated patients the HSG scores range from 0 to 100, with 30 patients having scores of 20.25 or less. In 12 treated patients the HSG scores vary from 0 to 61.9 with 7 out of 12 patients having scores of 21.94 or more. Hence, 37 out of 46 patients (80.4 per cent) can be identified as to whether or not they were administered certain therapies within four days prior to the HSG test. This dichotomous quantitative differentiation is highly significant, since the chi-square yields a value of 10.57 indicating that the probabilities are approximately 1 in 1000 that the observed dichotomy could have arisen as a result of random sampling errors.

DISCUSSION

1. *As to what Hematosonography measures:*

At this writing it should be stressed that the biologic elements which HSG measures are not as yet fully elucidated. It would appear as though the HSG measures dynamic physical changes in whole blood during the clotting process. What influence ultrasound itself exerts on the blood remains to be determined. That the HSG offers a moving profile of the effects of biochemical substances on the clotting process and that this method may be applicable to the study of many metabolic problems is only suggested and remains to be proved. That these leads must be investigated is indicated by the data we have presented. Conclusions as to how broad an applicablity hematosonography may have should be reserved pending the accumulation of large experience in many biologic fields. That hematosonography may be an important scientific technique for biologic quantitation has been demonstrated by our data. We cannot, however, overstress the need for restraint and caution in respect to any

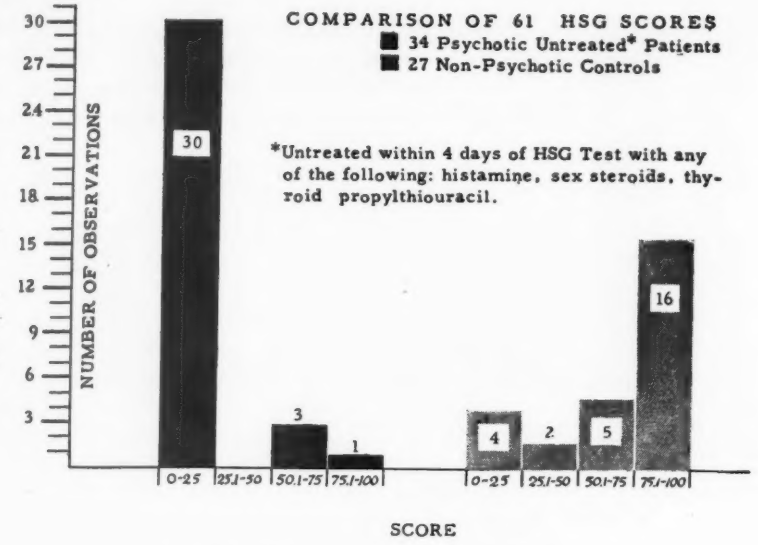

FIGURE II: Dichotomous Quantitative Differentiation of Untreated Patients from Controls = 88.5%; $\chi^2 = 36.04$

new development. Needless to say, our studies on hematosonography are going forward on a number of fronts in relation to its fundamental medical and biochemical applicability.

2. *As to standardization of procedures and calibration of equipment for hematosonography:*

Our experience has indicated that care and control are essential to the accuracy of the procedure. Seemingly trivial or seemingly unrelated changes can lead to confusing results and may lead to the necessity of reevaluation of factor quantitation.

3. *As to the accuracy of Hematosonography:*

It must be stressed that for this series 83.3 per cent accuracy is a minimal figure because—

a) the test was weighted against itself since the critical breakover points, for the factors were raised by the higher scores of most of the treated patients. This also weights the test more against the controls than against the patients;
b) no correcting factor for certain therapies was used to adjust for what has been demonstrated to be its deviating effect upon the score;
c) menstruation and upper respiratory infection were neither ruled out in the controls nor corrected for in the scoring; the data suggest that these conditions affect the scores.

4. *As to what Hematosonography does:*

At this juncture we would like to stress that the test does not give a clinical diagnosis. It has afforded a dichotomous quantitative differentiation of psychotic from nonpsychotic, and also of treated from untreated psychotic in the two series studied. This DQD has a high order of accuracy and a very high order of statistical significance.

The dichotomy between treated and untreated patients is very important for:

a) it lends support to the validity of the procedure used in scoring, since the original value weight and scores were set for dichotomization between patients and controls. When this same method was used as a means of identifying treated or untreated patients, it was found to be highly accurate.

b) it points to a common biophysical effect produced by thyroid, testosterone, histamine, and propylthiouracil. This is interesting in the light of a previous report which discussed physiologic common denominators of various therapies employed in psychiatry. Further study may elicit whether the ability to raise the HSG score is common to all the therapies currently utilized and whether there is an association between clinical improvement and attainment of a score which approaches or falls into the normal ranges. The conclusive demonstration of such association could provide psychiatry with a truly objective means of evaluating therapies.

c) it emphasized again the importance of a maintenance of therapy for psychoses which are truly chronic diseases. If the biophysical effects of therapy are not elicited when medication had been discontinued 4 days prior to testing, one may assume that these effects are in all likelihood transient. In order to maintain whatever beneficial attributes they may have, it may become necessary in many instances to continue therapy over extremely long periods. Clinical observation had led this group to similar conclusions previously.

It may be of interest to record at this point that a survey of 1505 consecutive necropsies performed at Creedmoor State Hospital (1932 to 1949) revealed the following:

2 prostatic carcinoma
3 prostatic fibrosis
2 prostatic hyperplasia
12 breast carcinoma

Of these, none occurred among the 236 schizophrenics autopsied. Carcinoma of the breast was found in 1 involutional melancholic. The importance of this is emphasized by the fact that the schizophrenias constituted approximately 40 per cent of the hospital population in

the years above mentioned. This may be of more than passing interest, for if schizophrenia is the result of hormonal dysequilibrations characterized by adrenocortical operative excess and hypogonadal and/or hypothyroid (etc.) operative deficiency (as was postulated in 1949 when the psychosis-producing effects of cortisone were predicted[5, 6]), then one would not expect to find metabolic diseases which are not associated with such hormonal imbalances. As an illustration, it has been shown[7] that the urine of schizophrenic males more closely approximates in its hormonal concentrations the urine of a normal female than that of a male. Thus, the usual incidence of prostatic carcinoma would not be expected in the schizophrenias. Similarly, if female schizophrenics have a relative adrenocortical and androgenic operative excess (viz. marked hirsutism) or a relative estrogenic operative deficiency, then breast carcinoma would not be likely to occur in the same frequency as in the general population. Since the HSG scores seem to be influenced by hormonal forces as revealed during medication, it would seem to follow that hematosonography may be informative when applied to blood studies of patients with prostatic and breast carcinoma.

In regard to the general problem of blood clotting and *in vivo* clotting as in coronary thrombosis and occlusion, it may be noted that the survey (referred to above) recorded 13 cases of coronary pathology. Of these, none occurred in schizophrenics. The ability to study more accurately the clotting process as afforded by HSG may here also permit the elucidation of the metabolic factors underlying the dissociation of coronary thrombosis and schizophrenia.

At the First International Congress of Psychiatry meeting in Paris last year we stated that, "We are today on the threshold of the era of metabolic medicine and metabolic psychiatry. This metabolic era is as full of promise as the concurrently developing atomic era is fraught with dangers. Through the metabolic era psychiatry will come to its fullest understanding of neuronal physiology and its relationship to psychodynamics. Predictability and control will become fundamental to a science of psychiatry in which modern physics, chemistry, and mathematics will be fused into a newer knowledge of the energetics and integration of the nervous system whose bizarre symptomatologic manifestations have fascinated and victimized man from time immemorial."[8] Our physiologic findings had led us inexorably to such conclusions. Yet, it was evident from the difficulties we had encountered that methods of precise quantitation are essential. We are grateful for the privilege of presenting one such which we hope will help carry us over the threshold into the era of "metabolic medicine" and "metabolic psychiatry."

SUMMARY

A. Investigation of the whole blood of 34 hospitalized and 12 nonhospitalized, treated and untreated psychotics and 27 controls have been carried out utilizing ultrasound as a quantitating modality of certain, as yet undefined, physical characteristics of clotting blood.

1. A difference between the hematosonographs (HSG) of psychotics and nonpsychotics, as a group, has been demonstrated—with a chi-square of 31.77.
2. A difference between the HSG scores of 34 untreated psychotics and of 12 treated psychotics has also been demonstrated with a chi-square of 10.57.

B. Following a factor analysis and properly weighted scores (without using correcting factors for therapy, menstruation, or upper respiratory infection), it is possible by dichotomous quantitated differentition (DQD)—
   1. to discriminate between patients and controls with an accuracy of 83.5 per cent.
   2. to identify patients correctly as such with an accuracy of 87 per cent.
   3. to identify correctly whether or not the patient is under certain treatments with an accuracy of 80.4 per cent.

C. The scores of patients who either were receiving or had, within 4 days of testing, received such substances as histamine, sex steroids, thyroid, and propylthiouracil and that of one patient 9 months postlobotomy were either higher and closer to the normal scores or actually scored within the control range. It may be of some significance that 3 out of 6 of the failures in identification were patients receiving these medications.

D. Hematosonography is *not*, in this report, presented as a perfected and absolute diagnostic technique in psychiatry. Endocrine disturbances, such as frank hypothyroidism or hypogonadism or other biochemical disturbances, might conceivably affect the accuracy of the HSG score in the differentiation of psychotics from nonpsychotics. This very consideration simultaneously suggests the potentialities of this new tool in the study of endocrine function, endocrinopathies, and other metabolic disorders as they are reflected through their influence upon blood clot behavior. The applicability of hematosonography for the observation and control of the effects of hormonal, metabolic and other therapies is forseeable.

CONCLUSIONS

These investigations have demonstrated:

1. The applicability of ultrasound in a new type of blood study—hematosonography (HSG).
2. The use of HSG to differentiate, with a high degree of accuracy (over 83 per cent) and statistical significance (chi-square of 31.77), psychotics from nonpsychotics by ultrasonic investigation of a blood sample. Thus, HSG
   a) has demonstrated a definitive biologic difference between psychotics and nonpsychotics;
   b) has afforded a measure for quantitating this difference, and
   c) is incorporating elements of the basic sciences of physics and mathematics into the methology of psychiatric research.
3. Hematosonography has further differentiated, with high accuracy (over 80 per cent) and statistical significance (chi-square of 10.57), psychotics receiving hista-

mine, thyroid, propylthiouracil, and sex steroids from those not receiving these therapies. Thus,

a) HSG supports previous evidences of common denominators in some of the therapies used in the psychoses; in this instance, elevated HSG scores are common to patients receiving these therapies.

b) In recording differences in patients receiving such substances, the HSG may, if further investigations are supportive, afford a valuable index to hormone and possibly other therapies.

c) By differentiating patients who were receiving therapy at the time of HSG from those who had not or who had received therapy up to four days prior to HSG, the procedure suggests that therapy must be maintained. The finding of elevated HSG scores (towards or into the normal range) in psychotic patients undergoing certain therapies points to physiological effects of these therapies which may eventually help correlate therapy and the results of therapy by affording objective criteria and indices.

4. The implications of hematosonography are so far-reaching in endocrinology and metabolic fields, as well as in other branches of medicine, biology and chemistry, that extensive exploration of this new acquisition of medical science is indicated.

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PROTOCOL OF FACTOR VALUES AND SCORING OF PATIENTS: SERIES I

Patient No.	Factor Value & Score	AB	Ccp	DE	Ecp	DEcp	Dcp	Ecp/Ccp	Total Score	Interpretation
1	2	3	4	5	6	7	8	9	10	11
619	v	40	21	1500	71	52.5	18	3.45		Psychosis
	s	0	*	0	0	0	*	0	0	Untreated
603	v	40	18	1500	40.5	24	17	2.02		Psychosis
	s	0	*	0	0	0	*	0	0	Untreated
625	v	40	18.5	1480	56.5	39.5	17	2.98		Psychosis
	s	0	*	0	0	0	*	0	0	Untreated
231	v	40	20	1300	64	38.5	18	3.12		Psychosis
	s	0	*	0	0	0	*	0	0	Untreated
623	v	40	19	1280	66	41.5	17.5	3.47		Psychosis
	s	0	*	0	0	0	*	0	0	Untreated
620	v	40	21	1360	70.5	52.5	18	3.36		Psychosis
	s	0	*	0	0	0	*	0	0	Untreated‡
211	v	40	18.5	1480	64	47.5	16.5	3.28		Psychosis
	s	0	*	0	0	0	*	0	0	Untreated
226	v	40	19.5	920	60.5	43	15.5	3.10		Psychosis
	s	0	*	0	0	0	*	0	0	Untreated
633	v	40	21	820	57	36	20	2.72		Psychosis
	s	0	*	0	0	0	*	0	0	Untreated
220	v	60	20	840	56.5	33	15.5	2.90		Psychosis
	s	18.06	*	0	0	0	*	0	18.06	Untreated
622	v	140	33.5	980	68	37.5	19.5	1.36		Psychosis
	s	18.06	*	0	0	0	*	0	18.06	Untreated‡
77	v	60	15.5	1480	54	48	14	3.48		Psychosis
	s	18.06	*	0	0	0	*	0	18.06	Untreated
134	v	80	13	780	46	21	15	2.56		Psychosis
	s	18.06	*	0	0	0	*	0	18.06	Untreated
624	v	60	18	980	59.5	32	15.5	3.30		Psychosis
	s	18.06	*	0	0	0	*	0	18.06	Untreated
630	v	60	17	1280	64	46.5	15.5	3.55		Psychosis
	s	18.06	*	0	0	0	*	0	18.06	Untreated
75	v	40	24	1760	66.5	45.5	20.5	2.76		Psychosis
	s	0	*	20	0	0	*	0	20	Untreated‡

v—Value as determined by measurement
s—Score as determined from table of weighted scores
*—This factor not used in scoring Series I
‡—Interpretation of therapy status incorrect

PROTOCOL OF FACTOR VALUES AND SCORING OF PATIENTS: SERIES I

Patient No.	Factor Value & Score	AB	Ccp	DE	Ecp	DEcp	Dcp	Ecp/Ccp	Total Score	Interpretation
1	2	3	4	5	6	7	8	9	10	11
85	v	40	22	1560	71	51.5	19.5	3.22		Psychosis
	s	0	*	20	0	0	*	0	20	Untreated‡
627	v	40	22	1620	70.5	51	19.5	3.20		Psychosis
	s	0	*	20	0	0	*	0	20	Untreated
168	v	20	24	1120	74.5	49	20	3.10		Psychosis
	s	0	*	0	20	0	*	0	20	Untreated
165	v	20	22	1680	69	48.5	20.5	3.14		Psychosis
	s	0	*	20	0	0	*	0	20	Untreated‡
140	v	20	18	1280	65	46.5	16.5	3.60		Psychosis
	s	0	*	0	0	0	*	21.94	21.94	Treated
138	v	40	20	1740	82	62	20	3.10		Psychosis
	s	0	*	20	20	0	*	0	40	Treated
618	v	40	22	1520	76	56.5	20.5	3.46		Psychosis
	s	0	*	0	20	0	*	0	40	Treated
626	v	40	19	1420	77	56.5	17.5	4.05		No Psychosis†
	s	0	*	0	20	20	*	21.94	61.94	—‡§
621	v	40	18.5	1280	73	56	17	3.74		No Psychosis†
	s	0	*	0	20	20	*	21.94	61.94	—
616	v	40	19.5	1520	80	61.5	18	4.10		No Psychosis†
	s	0	*	0	20	20	*	21.94	61.94	—
631	v	80	17.5	1520	73.5	57	16.5	4.20		No Psychosis†
	s	18.06	*	0	20	20	*	21.94	80	—‡
221	v	60	19	1620	72	54	18	3.78		No Psychosis†
	s	18.06	*	20	20	20	*	21.94	100	—‡

v—Value as determined by measurement
s—Score as determined from table of weighted scores
*—This factor not used in scoring Series I
†—Interpretation of clinical status incorrect
‡—Interpretation of therapy status incorrect
§—Topectomy

PROTOCOL OF FACTOR VALUES AND SCORING OF CONTROLS: SERIES I

Control No.	Factor Value & Score	AB	Ccp	DE	Ecp	DEcp	Dcp	Ecp/Ccp	Total Score	Interpretation
1	2	3	4	5	6	7	8	9	10	11
CL1	v	40	18.5	1660	66	48.5	17.5	3.47		Psychosis†
	s	0	*	20	0	0	*	0	20	—
CL2	v	80	18	1400	66	48.5	16	3.67		Psychosis†
	s	18.06	*	0	0	0	*	21.94	40	U.R.I.
CL3	v	60	17	1160	63	44.5	15.5	3.70		Psychosis†
F	s	18.06	*	0	0	0	*	21.94	40	Menses
CL4	v	80	17	1280	67	49	15.5	3.94		Psychosis†
F	s	18.06	*	0	0	0	*	21.94	40	U.R.I.
CL5A	v	60	18	1360	72	52.5	16.5	4.00		No Psychosis
	s	18.06	*	0	20	0	*	21.94	60	U.R.I.
CL2A	v	40	21	1560	71.5	54.5	17	3.48		No Psychosis
	s	0	*	20	20	20	*	0	60	
CL6	v	20	21.5	1460	78.5	59	19.5	3.64		No Psychosis
F	s	0	*	0	20	20	*	21.94	61.94	
CL7	v	60	21	1640	74	55	19	3.43		No Psychosis
	s	18.06	*	20	20	20	*	0	78.06	
CL8	v	60	20.5	1400	75.5	53.5	17.5	3.78		No Psychosis
	s	18.06	*	0	20	20	*	21.94	80	U.R.I.
CL9	v	40	20.5	1640	78.5	60.5	18	3.83		No Psychosis
	s	0	*	20	20	20	*	21.94	81.94	
CL5	v	40	18	1620	75.5	58.5	17	4.20		No Psychosis
	s	0	*	20	20	20	*	21.94	81.94	
CL8A	v	40	17	1560	74.5	58.5	16	4.37		No Psychosis
	s	0	*	20	20	20	*	21.94	81.94	
CL10	v	20	20.5	1620	73	53.5	19.5	3.60		No Psychosis
F	s	0	*	20	20	20	*	21.94	81.94	
CL11	v	60	20	1680	81	61	20	3.85		No Psychosis
	s	18.06	*	20	20	20	*	21.94	100	
CL12	v	60	19.5	1560	75	58.5	16.5	3.75		No Psychosis
	s	18.06	*	20	20	20	*	21.94	100	

v—Value as determined by measurement
s—Score as determined from table of weighted scores
*—This factor not used in scoring Series I.
†—Interpretation of clinical status incorrect
‡—Interpretation of therapy status incorrect
§—Topectomy
U.R.I.—Upper respiratory infection. F—Female.

PROTOCOL OF FACTOR VALUES AND SCORING OF PATIENTS: SERIES II

Patient No.	Factor Value & Score	AB	Ccp	DE	Ecp	DEcp	Dcp	Ecp/Ccp	Total Score	Interpretation
1	2	3	4	5	6	7	8	9	10	11
403	v	30	22.2	1710	83	62	21	3.73		Psychosis
	s	**	0	0	0	**	0	0	0	Untreated
602	v	30	22.5	1570	79	59	20	3.51		Psychosis
	s	**	0	0	0	**	0	0	0	Untreated
507	v	30	27.5	1710	83	58.5	24.5	3.01		Psychosis
	s	**	0	0	0	**	0	0	0	Untreated
508	v	30	24	1720	84.5	63	21.5	3.52		Psychosis
	s	**	0	0	0	**	0	0	0	Untreated
410	v	40	24	1580	86	65.5	20.5	3.58		Psychosis
	s	**	0	0	0	**	0	0	0	Untreated
634	v	20	22.5	1700	86	65.5	20.5	3.82		Psychosis
	s	**	0	0	0	**	0	0	0	Untreated§
605	v	20	27	1590	84	58	26	3.11		Psychosis
	s	**	0	0	0	**	0	0	0	Untreated¶
229	v	30	20	1510	77	58	19	3.85		Psychosis
	s	**	0	18.66	0	**	0	0	18.66	Untreated
V1A	v	70	20	1560	79	60	19	3.95		Psychosis
	s	**	0	18.66	0	**	0	0	18.66	Untreated
216	v	40	20	1440	77	58	19	3.85		Psychosis
	s	**	0	18.66	0	**	0	0	18.66	Untreated
28	v	80	21	1620	68.5	48.5	20	3.26		Psychosis
	s	**	0	0	19.46	**	0	0	19.46	Untreated
629	v	20	21.5	1590	93	71	22	4.32		Psychosis
	s	**	0	0	0	**	0	19.46	19.46	Untreated
231A	v	30	21	1700	87.5	68	19.5	4.16		Psychosis
	s	**	0	0	0	**	0	19.46	19.46	Untreated
632	v	20	22.5	1700	91	71	20	4.04		Psychosis
	s	**	0	0	0	**	0	19.46	19.46	Untreated§
635	v	40	22	1640	79	67	12	3.59		Psychosis
	s	**	0	0	0	**	20.25	0	20.25	Untreated
147	v	40	26.7	1520	73.5	55.5	18	2.75		Psychosis
	s	**	0	18.66	19.46	**	0	0	38.12	Treated
18	v	30	19.5	1570	74	62	12	3.79		Psychosis
	s	**	0	0	19.46	**	20.25	0	39.71	Treated
CL24	v	25	15	1720	76	62.5	13.5	5.06		Psychosis†
	s	**	22.17	0	0	**	20.25	19.46	61.88	—

v—Value as determined by measurement
s—Score as determined from table of weighted scores
*—This factor not used in scoring Series I
†—Interpretation of clinical status incorrect
‡—Interpretation of therapy status incorrect
§—Topectomy

PROTOCOL OF FACTOR VALUES AND SCORING OF CONTROLS: SERIES II

Control No.	Factor Value & Score	AB	Ccp	DE	Ecp	DEcp	Dcp	Ecp/Ccp	Total Score	Interpretation
1	2	3	4	5	6	7	8	9	10	11
CL13	v	60	25	1490	83	63.5	19.5	3.32		Psychosis‡
	s	**	0	18.66	0	**	0	0	18.66	
CL14	v	30	21.5	1200	81.5	61.5	20	3.79		Psychosis‡
	s	**	0	18.66	0	**	0	0	18.66	
CL15	v	30	17.5	1680	89.5	77.5	12	5.11		No Psychosis
	s	**	22.17	0	0	**	20.25	19.46	61.88	
CL2B	v	30	14	1420	48.2	36.7	11.5	3.44		No Psychosis
	s	**	22.17	18.66	19.46	**	20.25	0	80.54	
CL16	v	40	17.5	1440	81	65.5	15.5	4.62		No Psychosis
	s	**	22.17	18.66	0	**	20.25	19.46	80.54	
CL17	v	20	17.5	1560	83	68	15	4.74		No Psychosis
	s	**	22.17	18.66	0	**	20.25	19.46	80.54	
CL18	v	30	14	1600	74.5	62	12.5	5.32		No Psychosis
	s	**	22.17	0	19.46	**	20.25	19.46	81.34	
CL19	v	50	18.5	1570	73.5	61.5	12	3.97		No Psychosis
	s	**	22.17	0	19.46	**	20.25	19.46	81.34	
CL20	v	40	16	1720	73	59.75	13.5	4.56		No Psychosis
	s	**	22.17	0	19.46	**	20.25	19.46	81.34	
CL21	v	30	15	1550	68	55	13	4.53		No Psychosis
	s	**	22.17	18.66	19.46	**	20.25	19.46	100.0	
CL22	v	40	17	1510	69	55	14	4.05		No Psychosis
	s	**	22.17	18.66	19.46	**	20.25	19.46	100.0	
CL23	v	30	15.5	1530	75	59	16	4.83		No Psychosis
	s	**	22.17	18.66	19.46	**	20.25	19.46	100.0	

**—This factor not used in scoring Series II
§—Topectomy
v—Value as determined by measurement
s—Score as determined from table of weighted scores
*—This factor not used in scoring Series I
‡—Interpretation of therapy status incorrect

Discussion

QUANTITATED IDENTIFICATION OF PSYCHOSIS BY BLOOD SAMPLE

CHAIRMAN HARRY A. LA BURT

I recognize Dr. Angrist.

DR. ALFRED ANGRIST

I would want to say, for the record, that I have really been most impressed by the equipment and the development of these instruments and particularly from the standpoint of the application of the instruments to the study of the *process* of clotting. Having for many years been toying with the problem of clotting in some of the cruder formats of the instrumentation that have been available to us, I can see in this particular setup infinite possibilities of application. But, therein is one of my concerns as far as its application here tonight.

Of all the biological systems that we have to deal with in the human body, the process of clotting is one of the most complex. I don't know how many variables enter into it, with everything controlled to begin with, and that means controlling many of the factors which were here admittedly not controlled.

You are dealing with a complex biological and biochemical system in which at least ten different known specific ingredients enter, with activators and inhibitors, and most of the factors are still probably unknown; but those that are known are very complex and variable indeed, and subtle.

It would seem then, that before a test of this type is applied in the abstract, because that is what you have done, for "quantitated identification" and *diagnosis* of such intangible states as psychoses and the like, much fundamental work is needed. From the standpoint of known physical and chemical changes, as far as biological science has yet established, we should first take this beautiful instrument, as it has been developed, and apply it to the action of clotting under the known variables that have already been expressed and the known aberrations of clotting in disease. Learn something about the clotting mechanism before applying it pragmatically to diagnosis. If you can do that, you can make a most important contribution, and then with that information in hand, you can apply it to the variations that occur in the mentally disturbed patient or whatever your specific nomenclature may be.

I am mindful of numerous tests that have been devised by the use of blood in diagnosis. There was a man who achieved considerable fame, and then infamy, by the adaptation of a blood test, a method of clotting blood on a slide, and applying it to the diagnosis of cancer. He had many supporters. Recently, too, only within a few years—you are all aware of the famous Huggins test, applied to the diagnosis of cancer. It is nothing more than the application of the clotting or coagulation process. We don't hear of it any more. It has gone the way of all flesh.

I would also mention this fact, and I hope I am not taking too long. We have had in our hand, in the biology laboratory, a test that has stood the test of time under varying conditions—the ordinary Wasserman complement fixation and the precipitation tests,—and yet no laboratory man would state that they represent tests in the sense of diagnosing a group of patients who had syphilis as separated from a group who did not, because we know of the variations, no matter how selective you make your antigen or how specific. There is an overlap that will always occur in the biological processes because of subtle influences, as far as blood serum is concerned.

Let me just mention one or two that I can point out as important here. The nutrition of the patient was controlled, but that doesn't control your fibrinogen factor, thrombin levels, AC globulin, your thrombin inhibitors, the trypsin content of the blood, your antitrypsin and the various other inhibitory factors—all of these will play a part in the curve you have here. What is more promising is that, by prolonging the period of the process of clotting, you obtain a continuing curve; therein lies

probably the most important application to the understanding of the clotting mechanism. Unscramble some of these variables first by such curves, and then apply it all to the problem of dichotomizing analysis and diagnosis. That would seem the proper approach as I understand biological science, rather than the broad overall empirical application to a field that is empirical enough as it is. No mathematician or statistician can solve an equation with too many unknowns and comparable insufficient known factual data with unknown relationships.

I would say, by way of concluding, I do not mean to belittle this effort. I think it is a remarkable procedure to have even evaluated this group of cases by this means. I think that the instrumentation is most remarkable,—I have never been more amazed by a demonstration, and I have been in the laboratory field for the last twenty-five years. To repeat, I have never been more impressed. I have also been most impressed by the painstaking mathematical analysis of these curves. The possibilities are infinite, but they should be applied first to the more basic fundamental processes. Until we do that, we are selling our fundamental scientists down the river. We are putting them up a blind alley, instead of down the road that is going to branch out into most fertile fields.

I do wish to commend those who have brought to light the application of an instrument of this kind to the problem of blood clotting, than which there is no more complex mechanism that I know of, and for which we need every bit of help we can get in the understanding of its complexities.

CHAIRMAN LA BURT

Dr. Lang, who is Assistant Commissioner of the Department of Mental Hygiene in Albany, will you say a few words?

DR. H. B. LANG

Well, I have had the good fortune to have some advance information; so I have had a chance to collect some of my thoughts. The possibilities and the implications inherent in this test as it stands at the moment are rather frightening. I am convinced that the investigators have shown a statistical validity that can be accepted as of the present. For that reason there should be every support for further investigation.

We must, however, always keep a cautious side look available to ourselves. I put the biometrician on the spot by demanding proof, check, and recheck; then I had our own statistician go after him, and then our own statistician went after me. When we got all through with the day's argument, we were satisfied as to the soundness of the scoring and the results of the scoring. We cannot foresee what it means, nor what its full implication may be for psychiatry. It does represent for the moment a tool by which we can separate out at least two groups, possibly a third.

I myself am rather frightened at its predictability in treatment. That is something we have never had. We have had to rely on subjective opinion. Subjective evaluation in estimating healing, healing rate, level of recovery, or improvement sometimes are vitiated by our own personal involvement in the interpersonal relations. We cannot form an accurate scientific opinion. We can form a valid clinical observation, though. This gives us a precise tool. It is something that has been required in psychiatry and will be of unestimable value.

Dr. La Burt, it has been a pleasure to be here.

CHAIRMAN LA BURT

Thank you, Dr. Lang. We are deeply appreciative of your message tonight. It is heartening indeed. If there are no further questions or discussion, I shall ask Dr. Arthur Sackler to please close.

DR. ARTHUR M. SACKLER

Dr. Lang, in stating that he was frightened by the implications, expressed our own reaction when this material came through. We have, as you might have noted, very carefully refrained throughout

the whole course of the papers from going too far beyond the scope of psychiatry. We realize full well the implications which Dr. Angrist hinted at, and many of which we are eager to get at. However, work of that sort requires a considerable amount of equipment and material. Nonetheless, it is planned and will go forward.

We must point out that the present studies were preliminary and limited and revealed an accurate differential between blood of psychotic and nonpsychotic on the basis of physical and mathematical scoring.

We can also report that the scores are affected by medications, e.g., histamine and sex steroids. It is our hope that actual analysis of this material will enable us to indicate which factors are being altered by the different endocrine substances. Such identification could then enable us in turn to recognize relative deficiencies and develop guides for therapy. As most of you know, we have long been convinced of the relationship between endocrine disturbance and psychosis and pointed out two years ago that such a dysequilibration is, in our opinion, related to the pathogenic mechanism. At that time, on the basis of our findings, we predicted that cortisone and ACTH would produce psychosis.

I want to express the appreciation of our entire group to the State, to Drs. Bigelow, Lang and La Burt. This work would not have been possible without their support, and whatever merit there is in the work, I think a good measure of the credit is due to them.

CHAIRMAN LA BURT

I see one of our well-known Internists, Dr. Macfarlane. He must be able to contribute something to the discussion from the internal medical point of view.

DR. J. R. MACFARLANE

I haven't much to add. I did wonder, in taking blood from a group of undernourished or poorly nourished people, how that would be when compared to the controls?

DR. SACKLER

When we first got our results, we began to look for possible sources of error. One of the first possibilities considered was the nutritional status. It was then that we included a group of the out-patients with good nutritional status. Our accuracy of identification was higher than the in-patient group. Thus, in a way, we attempted to adjust for possible differences in hospitalized patients' nutritional status as compared to controls.

DR. MACFARLANE

I would like to add another thing. I have never been so impressed at a presentation of a paper, at the excellent coordination of mathematics, medicine, and psychiatry. I think it was a wonderful demonstration. I also feel, the fact that this instrument can and should be applied in the basic sciences does not change the real significance of the findings presented here tonight.

These men have not interpreted their findings in the light of the still not understood variations of the clotting mechanism. They have shown that, with a very high degree of accuracy, these graphs fall into identifiable patterns sufficiently characteristic that, without foreknowledge of the case under study, they can be used for the purpose of a diagnostic adjunct and possibly providing a key to information of complex and far-reaching importance. I think this is the thing we must consider here tonight in the critical evaluation of this paper.

CHAIRMAN LA BURT

May I express my thanks to each member of this group for being with us. I trust that your time has been well spent.